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(54) Title: NOVEL COMPOUNDS

(57) Abstract: Polypeptides and polynucleotides of the genes set forth in Table I and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing polypeptides and polynucleotides of the genes set forth in Table I in diagnostic assays.

## **Novel Compounds**

### **Field of Invention**

This invention relates to newly identified polypeptides and polynucleotides encoding such polypeptides, to their use in diagnosis and in identifying compounds that may be agonists, antagonists that are potentially useful in therapy, and to production of such polypeptides and polynucleotides. The polynucleotides and polypeptides of the present invention also relate to proteins with signal sequences which allow them to be secreted extracellularly or membrane-associated (hereinafter often referred collectively as secreted proteins or secreted polypeptides).

### **Background of the Invention**

The drug discovery process is currently undergoing a fundamental revolution as it embraces "functional genomics", that is, high throughput genome- or gene-based biology. This approach as a means to identify genes and gene products as therapeutic targets is rapidly superseding earlier approaches based on "positional cloning". A phenotype, that is a biological function or genetic disease, would be identified and this would then be tracked back to the responsible gene, based on its genetic map position.

Functional genomics relies heavily on high-throughput DNA sequencing technologies and the various tools of bioinformatics to identify gene sequences of potential interest from the many molecular biology databases now available. There is a continuing need to identify and characterise further genes and their related polypeptides/proteins, as targets for drug discovery.

Proteins and polypeptides that are naturally secreted into blood, lymph and other body fluids, or secreted into the cellular membrane are of primary interest for pharmaceutical research and development. The reason for this interest is the relative ease to target protein therapeutics into their place of action (body fluids or the cellular membrane). The natural pathway for protein secretion into extracellular space is the endoplasmic reticulum in eukaryotes and the inner membrane in prokaryotes (Palade, 1975, Science, 189, 347; Milstein, Brownlee, Harrison, and Mathews, 1972, Nature New Biol., 239, 117; Blobel, and Dobberstein, 1975, J. Cell. Biol., 67, 835). On the other hand, there is no known natural pathway for exporting a protein from the exterior of the cells into the cytosol (with the exception of pinocytosis, a mechanism of snake venom toxin intrusion into cells). Therefore targeting protein therapeutics into cells poses extreme difficulties.

The secreted and membrane-associated proteins include but are not limited to all peptide hormones and their receptors (including but not limited to insulin, growth hormones, chemokines, cytokines, neuropeptides, integrins, kallikreins, lamins,

melanins, natriuretic hormones, neuropsin, neurotrophins, pituitary hormones, pleiotropins, prostaglandins, secretogranins, selectins, thromboglobulins, thymosins), the breast and colon cancer gene products, leptin, the obesity gene protein and its receptors, serum albumin, superoxide dismutase, spliceosome proteins, 7TM (transmembrane) proteins also called as G-protein coupled receptors, immunoglobulins, several families of serine proteinases (including but not limited to proteins of the blood coagulation cascade, digestive enzymes), deoxyribonuclease I, etc.

Therapeutics based on secreted or membrane-associated proteins approved by FDA or foreign agencies include but are not limited to insulin, glucagon, growth hormone, chorionic gonadotropin, follicle stimulating hormone, luteinizing hormone, calcitonin, adrenocorticotrophic hormone (ACTH), vasopressin, interleukines, interferones, immunoglobulins, lactoferrin (diverse products marketed by several companies), tissue-type plasminogen activator (Alteplase by Genentech), hyaluronidase (Wydase by Wyeth-Ayerst), dornase alpha (Pulmozyme by Genentech), Chymodiactin (chymopapain by Knoll), alglucerase (Ceredase by Genzyme), streptokinase (Kabikinase by Pharmacia) (Streptase by Astra), etc. This indicates that secreted and membrane-associated proteins have an established, proven history as therapeutic targets. Clearly, there is a need for identification and characterization of further secreted and membrane-associated proteins which can play a role in preventing, ameliorating or correcting dysfunction or disease, including but not limited to diabetes, breast-, prostate-, colon cancer and other malignant tumors, hyper- and hypotension, obesity, bulimia, anorexia, growth abnormalities, asthma, manic depression, dementia, delirium, mental retardation, Huntington's disease, Tourette's syndrome, schizophrenia, growth, mental or sexual development disorders, and dysfunctions of the blood cascade system including those leading to stroke. The proteins of the present invention which include the signal sequences are also useful to further elucidate the mechanism of protein transport which at present is not entirely understood, and thus can be used as research tools.

### **Summary of the Invention**

The present invention relates to particular polypeptides and polynucleotides of the genes set forth in Table I, including recombinant materials and methods for their production. Such polypeptides and polynucleotides are of interest in relation to methods of treatment of certain diseases, including, but not limited to, the diseases set forth in Tables III and V,

hereinafter referred to as "diseases of the invention". In a further aspect, the invention relates to methods for identifying agonists and antagonists (*e.g.*, inhibitors) using the materials provided by the invention, and treating conditions associated with imbalance of polypeptides and/or polynucleotides of the genes set forth in Table I with the identified compounds. In still a further aspect, the invention relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels the genes set forth in Table I. Another aspect of the invention concerns a polynucleotide comprising any of the nucleotide sequences set forth in the Sequence Listing and a polypeptide comprising a polypeptide encoded by the nucleotide sequence. In another aspect, the invention relates to a polypeptide comprising any of the polypeptide sequences set forth in the Sequence Listing and recombinant materials and methods for their production. Another aspect of the invention relates to methods for using such polypeptides and polynucleotides. Such uses include the treatment of diseases, abnormalities and disorders (hereinafter simply referred to as diseases) caused by abnormal expression, production, function and or metabolism of the genes of this invention, and such diseases are readily apparent by those skilled in the art from the homology to other proteins disclosed for each attached sequence. In still another aspect, the invention relates to methods to identify agonists and antagonists using the materials provided by the invention, and treating conditions associated with the imbalance with the identified compounds. Yet another aspect of the invention relates to diagnostic assays for detecting diseases associated with inappropriate activity or levels of the secreted proteins of the present invention.

#### **Description of the Invention**

In a first aspect, the present invention relates to polypeptides the genes set forth in Table I. Such polypeptides include:

- (a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in the Sequence Listing, herein when referring to polynucleotides or polypeptides of the Sequence Listing, a reference is also made to the Sequence Listing referred to in the Sequence Listing;
- (b) an isolated polypeptide comprising a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;
- (c) an isolated polypeptide comprising a polypeptide sequence set forth in the Sequence Listing;
- (d) an isolated polypeptide having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;
- (e) a polypeptide sequence set forth in the Sequence Listing; and

(f) an isolated polypeptide having or comprising a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing;

(g) fragments and variants of such polypeptides in (a) to (f).

Polypeptides of the present invention are believed to be members of the gene families set forth in Table II. They are therefore of therapeutic and diagnostic interest for the reasons set forth in Tables III and V. The biological properties of the polypeptides and polynucleotides of the genes set forth in Table I are hereinafter referred to as "the biological activity" of polypeptides and polynucleotides of the genes set forth in Table I. Preferably, a polypeptide of the present invention exhibits at least one biological activity of the genes set forth in Table I.

Polypeptides of the present invention also include variants of the aforementioned polypeptides, including all allelic forms and splice variants. Such polypeptides vary from the reference polypeptide by insertions, deletions, and substitutions that may be conservative or non-conservative, or any combination thereof. Particularly preferred variants are those in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acids are inserted, substituted, or deleted, in any combination.

Preferred fragments of polypeptides of the present invention include an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids from an amino acid sequence set forth in the Sequence Listing, or an isolated polypeptide comprising an amino acid sequence having at least 30, 50 or 100 contiguous amino acids truncated or deleted from an amino acid sequence set forth in the Sequence Listing. Preferred fragments are biologically active fragments that mediate the biological activity of polypeptides and polynucleotides of the genes set forth in Table I, including those with a similar activity or an improved activity, or with a decreased undesirable activity. Also preferred are those fragments that are antigenic or immunogenic in an animal, especially in a human.

Fragments of a polypeptide of the invention may be employed for producing the corresponding full-length polypeptide by peptide synthesis; therefore, these variants may be employed as intermediates for producing the full-length polypeptides of the invention. A polypeptide of the present invention may be in the form of the "mature" protein or may be a part of a larger protein such as a precursor or a fusion protein. It is often advantageous to include an additional amino acid sequence that contains secretory or leader sequences, pro-sequences,

sequences that aid in purification, for instance multiple histidine residues, or an additional sequence for stability during recombinant production.

Polypeptides of the present invention can be prepared in any suitable manner, for instance by isolation from naturally occurring sources, from genetically engineered host cells comprising expression systems (*vide infra*) or by chemical synthesis, using for instance automated peptide synthesizers, or a combination of such methods. Means for preparing such polypeptides are well understood in the art.

In a further aspect, the present invention relates to polynucleotides of the genes set forth in Table I. Such polynucleotides include:

- (a) an isolated polynucleotide comprising a polynucleotide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide sequence set forth in the Sequence Listing;
  - (b) an isolated polynucleotide comprising a polynucleotide set forth in the Sequence Listing;
  - (c) an isolated polynucleotide having at least 95%, 96%, 97%, 98%, or 99% identity to a polynucleotide set forth in the Sequence Listing;
  - (d) an isolated polynucleotide set forth in the Sequence Listing;
  - (e) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;
  - (f) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing;
  - (g) an isolated polynucleotide having a polynucleotide sequence encoding a polypeptide sequence having at least 95%, 96%, 97%, 98%, or 99% identity to a polypeptide sequence set forth in the Sequence Listing;
  - (h) an isolated polynucleotide encoding a polypeptide set forth in the Sequence Listing;
  - (i) an isolated polynucleotide having or comprising a polynucleotide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polynucleotide sequence set forth in the Sequence Listing;
  - (j) an isolated polynucleotide having or comprising a polynucleotide sequence encoding a polypeptide sequence that has an Identity Index of 0.95, 0.96, 0.97, 0.98, or 0.99 compared to a polypeptide sequence set forth in the Sequence Listing; and
- polynucleotides that are fragments and variants of the above mentioned polynucleotides or that are complementary to above mentioned polynucleotides, over the entire length thereof.

Preferred fragments of polynucleotides of the present invention include an isolated polynucleotide comprising an nucleotide sequence having at least 15, 30, 50 or 100 contiguous nucleotides from a sequence set forth in the Sequence Listing, or an isolated polynucleotide comprising a sequence having at least 30, 50 or 100 contiguous nucleotides truncated or deleted from a sequence set forth in the Sequence Listing.

Preferred variants of polynucleotides of the present invention include splice variants, allelic variants, and polymorphisms, including polynucleotides having one or more single nucleotide polymorphisms (SNPs).

Polynucleotides of the present invention also include polynucleotides encoding polypeptide variants that comprise an amino acid sequence set forth in the Sequence Listing and in which several, for instance from 50 to 30, from 30 to 20, from 20 to 10, from 10 to 5, from 5 to 3, from 3 to 2, from 2 to 1 or 1 amino acid residues are substituted, deleted or added, in any combination.

In a further aspect, the present invention provides polynucleotides that are RNA transcripts of the DNA sequences of the present invention. Accordingly, there is provided an RNA polynucleotide that:

(a) comprises an RNA transcript of the DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(b) is a RNA transcript of a DNA sequence encoding a polypeptide set forth in the Sequence Listing;

(c) comprises an RNA transcript of a DNA sequence set forth in the Sequence Listing;

or

(d) is a RNA transcript of a DNA sequence set forth in the Sequence Listing; and RNA polynucleotides that are complementary thereto.

The polynucleotide sequences set forth in the Sequence Listing show homology with the polynucleotide sequences set forth in Table II. A polynucleotide sequence set forth in the Sequence Listing is a cDNA sequence that encodes a polypeptide set forth in the Sequence Listing. A polynucleotide sequence encoding a polypeptide set forth in the Sequence Listing may be identical to a polypeptide encoding a sequence set forth in the Sequence Listing or it may be a sequence other than a sequence set forth in the Sequence Listing, which, as a result of the redundancy (degeneracy) of the genetic code, also encodes a polypeptide set forth in the Sequence Listing. A polypeptide of a sequence set forth in the Sequence Listing is related to

other proteins of the gene families set forth in Table II, having homology and/or structural similarity with the polypeptides set forth in Table II. Preferred polypeptides and polynucleotides of the present invention are expected to have, *inter alia*, similar biological functions/properties to their homologous polypeptides and polynucleotides. Furthermore, preferred polypeptides and polynucleotides of the present invention have at least one activity of the genes set forth in Table I.

Polynucleotides of the present invention may be obtained using standard cloning and screening techniques from a cDNA library derived from mRNA from the tissues set forth in Table IV (see for instance, Sambrook *et al.*, Molecular Cloning: A Laboratory Manual, 2nd Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). Polynucleotides of the invention can also be obtained from natural sources such as genomic DNA libraries or can be synthesized using well known and commercially available techniques.

When polynucleotides of the present invention are used for the recombinant production of polypeptides of the present invention, the polynucleotide may include the coding sequence for the mature polypeptide, by itself, or the coding sequence for the mature polypeptide in reading frame with other coding sequences, such as those encoding a leader or secretory sequence, a pre-, or pro- or prepro- protein sequence, or other fusion peptide portions. For example, a marker sequence that facilitates purification of the fused polypeptide can be encoded. In certain preferred embodiments of this aspect of the invention, the marker sequence is a hexa-histidine peptide, as provided in the pQE vector (Qiagen, Inc.) and described in Gentz *et al.*, Proc Natl Acad Sci USA (1989) 86:821-824, or is an HA tag. A polynucleotide may also contain non-coding 5' and 3' sequences, such as transcribed, non-translated sequences, splicing and polyadenylation signals, ribosome binding sites and sequences that stabilize mRNA.

Polynucleotides that are identical, or have sufficient identity to a polynucleotide sequence set forth in the Sequence Listing, may be used as hybridization probes for cDNA and genomic DNA or as primers for a nucleic acid amplification reaction (for instance, PCR). Such probes and primers may be used to isolate full-length cDNAs and genomic clones encoding polypeptides of the present invention and to isolate cDNA and genomic clones of other genes (including genes encoding paralogs from human sources and orthologs and paralogs from species other than ) that have a high sequence similarity to sequences set forth in the Sequence Listing, typically at least 95% identity. Preferred probes and primers will generally comprise at least 15 nucleotides, preferably, at least 30 nucleotides and may have at least 50, if not at least



100 nucleotides. Particularly preferred probes will have between 30 and 50 nucleotides. Particularly preferred primers will have between 20 and 25 nucleotides.

A polynucleotide encoding a polypeptide of the present invention, including homologs from species other than , may be obtained by a process comprising the steps of screening a library under stringent hybridization conditions with a labeled probe having a sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides; and isolating full-length cDNA and genomic clones containing the polynucleotide sequence set forth in the Sequence Listing. Such hybridization techniques are well known to the skilled artisan. Preferred stringent hybridization conditions include overnight incubation at 42°C in a solution comprising: 50% formamide, 5xSSC (150mM NaCl, 15mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5x Denhardt's solution, 10 % dextran sulfate, and 20 microgram/ml denatured, sheared salmon sperm DNA; followed by washing the filters in 0.1x SSC at about 65°C. Thus the present invention also includes isolated polynucleotides, preferably with a nucleotide sequence of at least 100, obtained by screening a library under stringent hybridization conditions with a labeled probe having the sequence set forth in the Sequence Listing or a fragment thereof, preferably of at least 15 nucleotides.

The skilled artisan will appreciate that, in many cases, an isolated cDNA sequence will be incomplete, in that the region coding for the polypeptide does not extend all the way through to the 5' terminus. This is a consequence of reverse transcriptase, an enzyme with inherently low "processivity" (a measure of the ability of the enzyme to remain attached to the template during the polymerisation reaction), failing to complete a DNA copy of the mRNA template during first strand cDNA synthesis.

There are several methods available and well known to those skilled in the art to obtain full-length cDNAs, or extend short cDNAs, for example those based on the method of Rapid Amplification of cDNA ends (RACE) (see, for example, Frohman et al., Proc Nat Acad Sci USA 85, 8998-9002, 1988). Recent modifications of the technique, exemplified by the Marathon (trade mark) technology (Clontech Laboratories Inc.) for example, have significantly simplified the search for longer cDNAs. In the Marathon (trade mark) technology, cDNAs have been prepared from mRNA extracted from a chosen tissue and an 'adaptor' sequence ligated onto each end. Nucleic acid amplification (PCR) is then carried out to amplify the "missing" 5' end of the cDNA using a combination of gene specific and adaptor specific oligonucleotide primers. The PCR reaction is then repeated using 'nested' primers, that is, primers designed to

anneal within the amplified product (typically an adapter specific primer that anneals further 3' in the adaptor sequence and a gene specific primer that anneals further 5' in the known gene sequence). The products of this reaction can then be analyzed by DNA sequencing and a full-length cDNA constructed either by joining the product directly to the existing cDNA to give a complete sequence, or carrying out a separate full-length PCR using the new sequence information for the design of the 5' primer.

Recombinant polypeptides of the present invention may be prepared by processes well known in the art from genetically engineered host cells comprising expression systems. Accordingly, in a further aspect, the present invention relates to expression systems comprising a polynucleotide or polynucleotides of the present invention, to host cells which are genetically engineered with such expression systems and to the production of polypeptides of the invention by recombinant techniques. Cell-free translation systems can also be employed to produce such proteins using RNAs derived from the DNA constructs of the present invention.

For recombinant production, host cells can be genetically engineered to incorporate expression systems or portions thereof for polynucleotides of the present invention. Polynucleotides may be introduced into host cells by methods described in many standard laboratory manuals, such as Davis et al., Basic Methods in Molecular Biology (1986) and Sambrook *et al.* (*ibid*). Preferred methods of introducing polynucleotides into host cells include, for instance, calcium phosphate transfection, DEAE-dextran mediated transfection, transfection, micro-injection, cationic lipid-mediated transfection, electroporation, transduction, scrape loading, ballistic introduction or infection.

Representative examples of appropriate hosts include bacterial cells, such as *Streptococci*, *Staphylococci*, *E. coli*, *Streptomyces* and *Bacillus subtilis* cells; fungal cells, such as yeast cells and *Aspergillus* cells; insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, HeLa, C127, 3T3, BHK, HEK 293 and Bowes melanoma cells; and plant cells.

A great variety of expression systems can be used, for instance, chromosomal, episomal and virus-derived systems, *e.g.*, vectors derived from bacterial plasmids, from bacteriophage, from transposons, from yeast episomes, from insertion elements, from yeast chromosomal elements, from viruses such as baculoviruses, papova viruses, such as SV40, vaccinia viruses, adenoviruses, fowl pox viruses, pseudorabies viruses and retroviruses, and vectors derived from combinations thereof, such as those derived from plasmid and bacteriophage genetic elements,

such as cosmids and phagemids. The expression systems may contain control regions that regulate as well as engender expression. Generally, any system or vector that is able to maintain, propagate or express a polynucleotide to produce a polypeptide in a host may be used. The appropriate polynucleotide sequence may be inserted into an expression system by any of a variety of well-known and routine techniques, such as, for example, those set forth in Sambrook *et al.*, (*ibid*). Appropriate secretion signals may be incorporated into the desired polypeptide to allow secretion of the translated protein into the lumen of the endoplasmic reticulum, the periplasmic space or the extracellular environment. These signals may be endogenous to the polypeptide or they may be heterologous signals.

If a polypeptide of the present invention is to be expressed for use in screening assays, it is generally preferred that the polypeptide be produced at the surface of the cell. In this event, the cells may be harvested prior to use in the screening assay. If the polypeptide is secreted into the medium, the medium can be recovered in order to recover and purify the polypeptide. If produced intracellularly, the cells must first be lysed before the polypeptide is recovered.

Polypeptides of the present invention can be recovered and purified from recombinant cell cultures by well-known methods including ammonium sulfate or ethanol precipitation, acid extraction, anion or cation exchange chromatography, phosphocellulose chromatography, hydrophobic interaction chromatography, affinity chromatography, hydroxylapatite chromatography and lectin chromatography. Most preferably, high performance liquid chromatography is employed for purification. Well known techniques for refolding proteins may be employed to regenerate active conformation when the polypeptide is denatured during intracellular synthesis, isolation and/or purification.

Polynucleotides of the present invention may be used as diagnostic reagents, through detecting mutations in the associated gene. Detection of a mutated form of a gene is characterized by the polynucleotides set forth in the Sequence Listing in the cDNA or genomic sequence and which is associated with a dysfunction. Will provide a diagnostic tool that can add to, or define, a diagnosis of a disease, or susceptibility to a disease, which results from under-expression, over-expression or altered spatial or temporal expression of the gene. Individuals carrying mutations in the gene may be detected at the DNA level by a variety of techniques well known in the art.

Nucleic acids for diagnosis may be obtained from a subject's cells, such as from blood, urine, saliva, tissue biopsy or autopsy material. The genomic DNA may be used directly for

detection or it may be amplified enzymatically by using PCR, preferably RT-PCR, or other amplification techniques prior to analysis. RNA or cDNA may also be used in similar fashion. Deletions and insertions can be detected by a change in size of the amplified product in comparison to the normal genotype. Point mutations can be identified by hybridizing amplified DNA to labeled nucleotide sequences of the genes set forth in Table I. Perfectly matched sequences can be distinguished from mismatched duplexes by RNase digestion or by differences in melting temperatures. DNA sequence difference may also be detected by alterations in the electrophoretic mobility of DNA fragments in gels, with or without denaturing agents, or by direct DNA sequencing (see, for instance, Myers *et al.*, Science (1985) 230:1242). Sequence changes at specific locations may also be revealed by nuclease protection assays, such as RNase and S1 protection or the chemical cleavage method (see Cotton *et al.*, Proc Natl Acad Sci USA (1985) 85: 4397-4401).

An array of oligonucleotide probes comprising polynucleotide sequences or fragments thereof of the genes set forth in Table I can be constructed to conduct efficient screening of *e.g.*, genetic mutations. Such arrays are preferably high density arrays or grids. Array technology methods are well known and have general applicability and can be used to address a variety of questions in molecular genetics including gene expression, genetic linkage, and genetic variability, see, for example, M. Chee *et al.*, Science, 274, 610-613 (1996) and other references cited therein.

Detection of abnormally decreased or increased levels of polypeptide or mRNA expression may also be used for diagnosing or determining susceptibility of a subject to a disease of the invention. Decreased or increased expression can be measured at the RNA level using any of the methods well known in the art for the quantitation of polynucleotides, such as, for example, nucleic acid amplification, for instance PCR, RT-PCR, RNase protection, Northern blotting and other hybridization methods. Assay techniques that can be used to determine levels of a protein, such as a polypeptide of the present invention, in a sample derived from a host are well-known to those of skill in the art. Such assay methods include radio-immunoassays, competitive-binding assays, Western Blot analysis and ELISA assays.

Thus in another aspect, the present invention relates to a diagnostic kit comprising:

- (a) a polynucleotide of the present invention, preferably the nucleotide sequence set forth in the Sequence Listing, or a fragment or an RNA transcript thereof;
- (b) a nucleotide sequence complementary to that of (a);

- (c) a polypeptide of the present invention, preferably the polypeptide set forth in the Sequence Listing or a fragment thereof; or
- (d) an antibody to a polypeptide of the present invention, preferably to the polypeptide set forth in the Sequence Listing .

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component. Such a kit will be of use in diagnosing a disease or susceptibility to a disease, particularly diseases of the invention, amongst others.

The polynucleotide sequences of the present invention are valuable for chromosome localisation studies. The sequences set forth in the Sequence Listing are specifically targeted to, and can hybridize with, a particular location on an individual human chromosome. The mapping of relevant sequences to chromosomes according to the present invention is an important first step in correlating those sequences with gene associated disease. Once a sequence has been mapped to a precise chromosomal location, the physical position of the sequence on the chromosome can be correlated with genetic map data. Such data are found in, for example, V. McKusick, Mendelian Inheritance in Man (available on-line through Johns Hopkins University Welch Medical Library). The relationship between genes and diseases that have been mapped to the same chromosomal region are then identified through linkage analysis (co-inheritance of physically adjacent genes). Precise human chromosomal localisations for a genomic sequence (gene fragment etc.) can be determined using Radiation Hybrid (RH) Mapping (Walter, M. Spillett, D., Thomas, P., Weissenbach, J., and Goodfellow, P., (1994) A method for constructing radiation hybrid maps of whole genomes, Nature Genetics 7, 22-28). A number of RH panels are available from Research Genetics (Huntsville, AL, USA) e.g. the GeneBridge4 RH panel (Hum Mol Genet 1996 Mar;5(3):339-46 A radiation hybrid map of the human genome. Gyapay G, Schmitt K, Fizames C, Jones H, Vega-Czarny N, Spillett D, Muselet D, Prud'Homme JF, Dib C, Auffray C, Morissette J, Weissenbach J, Goodfellow PN). To determine the chromosomal location of a gene using this panel, 93 PCRs are performed using primers designed from the gene of interest on RH DNAs. Each of these DNAs contains random human genomic fragments maintained in a hamster background (human / hamster hybrid cell lines). These PCRs result in 93 scores indicating the presence or absence of the PCR product of the gene of interest. These scores are compared with scores created using PCR products from genomic sequences of known location. This comparison is conducted at <http://www.genome.wi.mit.edu/>.

The polynucleotide sequences of the present invention are also valuable tools for tissue expression studies. Such studies allow the determination of expression patterns of polynucleotides of the present invention which may give an indication as to the expression patterns of the encoded polypeptides in tissues, by detecting the mRNAs that encode them. The techniques used are well known in the art and include in situ hybridization techniques to clones arrayed on a grid, such as cDNA microarray hybridization (Schena *et al*, Science, 270, 467-470, 1995 and Shalon *et al*, Genome Res, 6, 639-645, 1996) and nucleotide amplification techniques such as PCR. A preferred method uses the TAQMAN (Trade mark) technology available from Perkin Elmer. Results from these studies can provide an indication of the normal function of the polypeptide in the organism. In addition, comparative studies of the normal expression pattern of mRNAs with that of mRNAs encoded by an alternative form of the same gene (for example, one having an alteration in polypeptide coding potential or a regulatory mutation) can provide valuable insights into the role of the polypeptides of the present invention, or that of inappropriate expression thereof in disease. Such inappropriate expression may be of a temporal, spatial or simply quantitative nature.

A further aspect of the present invention relates to antibodies. The polypeptides of the invention or their fragments, or cells expressing them, can be used as immunogens to produce antibodies that are immunospecific for polypeptides of the present invention. The term "immunospecific" means that the antibodies have substantially greater affinity for the polypeptides of the invention than their affinity for other related polypeptides in the prior art.

Antibodies generated against polypeptides of the present invention may be obtained by administering the polypeptides or epitope-bearing fragments, or cells to an animal, preferably a non-human animal, using routine protocols. For preparation of monoclonal antibodies, any technique which provides antibodies produced by continuous cell line cultures can be used. Examples include the hybridoma technique (Kohler, G. and Milstein, C., Nature (1975) 256:495-497), the trioma technique, the human B-cell hybridoma technique (Kozbor *et al*, Immunology Today (1983) 4:72) and the EBV-hybridoma technique (Cole *et al*, Monoclonal Antibodies and Cancer Therapy, 77-96, Alan R. Liss, Inc., 1985).

Techniques for the production of single chain antibodies, such as those described in U.S. Patent No. 4,946,778, can also be adapted to produce single chain antibodies to polypeptides of this invention. Also, transgenic mice, or other organisms, including other mammals, may be used to express humanized antibodies.

The above-described antibodies may be employed to isolate or to identify clones expressing the polypeptide or to purify the polypeptides by affinity chromatography. Antibodies against polypeptides of the present invention may also be employed to treat diseases of the invention, amongst others.

Polypeptides and polynucleotides of the present invention may also be used as vaccines. Accordingly, in a further aspect, the present invention relates to a method for inducing an immunological response in a mammal that comprises inoculating the mammal with a polypeptide of the present invention, adequate to produce antibody and/or T cell immune response, including, for example, cytokine-producing T cells or cytotoxic T cells, to protect said animal from disease, whether that disease is already established within the individual or not. An immunological response in a mammal may also be induced by a method comprises delivering a polypeptide of the present invention *via* a vector directing expression of the polynucleotide and coding for the polypeptide *in vivo* in order to induce such an immunological response to produce antibody to protect said animal from diseases of the invention. One way of administering the vector is by accelerating it into the desired cells as a coating on particles or otherwise. Such nucleic acid vector may comprise DNA, RNA, a modified nucleic acid, or a DNA/RNA hybrid. For use a vaccine, a polypeptide or a nucleic acid vector will be normally provided as a vaccine formulation (composition). The formulation may further comprise a suitable carrier. Since a polypeptide may be broken down in the stomach, it is preferably administered parenterally (for instance, subcutaneous, intra-muscular, intravenous, or intra-dermal injection). Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions that may contain anti-oxidants, buffers, bacteriostats and solutes that render the formulation isotonic with the blood of the recipient; and aqueous and non-aqueous sterile suspensions that may include suspending agents or thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example, sealed ampoules and vials and may be stored in a freeze-dried condition requiring only the addition of the sterile liquid carrier immediately prior to use. The vaccine formulation may also include adjuvant systems for enhancing the immunogenicity of the formulation, such as oil-in water systems and other systems known in the art. The dosage will depend on the specific activity of the vaccine and can be readily determined by routine experimentation.

Polypeptides of the present invention have one or more biological functions that are of relevance in one or more disease states, in particular the diseases of the invention hereinbefore

mentioned. It is therefore useful to identify compounds that stimulate or inhibit the function or level of the polypeptide. Accordingly, in a further aspect, the present invention provides for a method of screening compounds to identify those that stimulate or inhibit the function or level of the polypeptide. Such methods identify agonists or antagonists that may be employed for therapeutic and prophylactic purposes for such diseases of the invention as hereinbefore mentioned. Compounds may be identified from a variety of sources, for example, cells, cell-free preparations, chemical libraries, collections of chemical compounds, and natural product mixtures. Such agonists or antagonists so-identified may be natural or modified substrates, ligands, receptors, enzymes, etc., as the case may be, of the polypeptide; a structural or functional mimetic thereof (see Coligan *et al.*, Current Protocols in Immunology 1(2):Chapter 5 (1991)) or a small molecule. Such small molecules preferably have a molecular weight below 2,000 daltons, more preferably between 300 and 1,000 daltons, and most preferably between 400 and 700 daltons. It is preferred that these small molecules are organic molecules.

The screening method may simply measure the binding of a candidate compound to the polypeptide, or to cells or membranes bearing the polypeptide, or a fusion protein thereof, by means of a label directly or indirectly associated with the candidate compound. Alternatively, the screening method may involve measuring or detecting (qualitatively or quantitatively) the competitive binding of a candidate compound to the polypeptide against a labeled competitor (*e.g.* agonist or antagonist). Further, these screening methods may test whether the candidate compound results in a signal generated by activation or inhibition of the polypeptide, using detection systems appropriate to the cells bearing the polypeptide. Inhibitors of activation are generally assayed in the presence of a known agonist and the effect on activation by the agonist by the presence of the candidate compound is observed. Further, the screening methods may simply comprise the steps of mixing a candidate compound with a solution containing a polypeptide of the present invention, to form a mixture, measuring an activity of the genes set forth in Table I in the mixture, and comparing activity of the mixture of the genes set forth in Table I to a control mixture which contains no candidate compound.

Polypeptides of the present invention may be employed in conventional low capacity screening methods and also in high-throughput screening (HTS) formats. Such HTS formats include not only the well-established use of 96- and, more recently, 384-well micotiter plates but also emerging methods such as the nanowell method described by Schullek *et al.*, Anal Biochem., 246, 20-29, (1997).



Fusion proteins, such as those made from Fc portion and polypeptide of the genes set forth in Table I, as hereinbefore described, can also be used for high-throughput screening assays to identify antagonists for the polypeptide of the present invention (see D. Bennett *et al.*, J Mol Recognition, 8:52-58 (1995); and K. Johanson *et al.*, J Biol Chem, 270(16):9459-9471 (1995)).

The polynucleotides, polypeptides and antibodies to the polypeptide of the present invention may also be used to configure screening methods for detecting the effect of added compounds on the production of mRNA and polypeptide in cells. For example, an ELISA assay may be constructed for measuring secreted or cell associated levels of polypeptide using monoclonal and polyclonal antibodies by standard methods known in the art. This can be used to discover agents that may inhibit or enhance the production of polypeptide (also called antagonist or agonist, respectively) from suitably manipulated cells or tissues.

A polypeptide of the present invention may be used to identify membrane bound or soluble receptors, if any, through standard receptor binding techniques known in the art. These include, but are not limited to, ligand binding and crosslinking assays in which the polypeptide is labeled with a radioactive isotope (for instance,  $^{125}\text{I}$ ), chemically modified (for instance, biotinylated), or fused to a peptide sequence suitable for detection or purification, and incubated with a source of the putative receptor (cells, cell membranes, cell supernatants, tissue extracts, bodily fluids). Other methods include biophysical techniques such as surface plasmon resonance and spectroscopy. These screening methods may also be used to identify agonists and antagonists of the polypeptide that compete with the binding of the polypeptide to its receptors, if any. Standard methods for conducting such assays are well understood in the art.

Examples of antagonists of polypeptides of the present invention include antibodies or, in some cases, oligonucleotides or proteins that are closely related to the ligands, substrates, receptors, enzymes, etc., as the case may be, of the polypeptide, *e.g.*, a fragment of the ligands, substrates, receptors, enzymes, etc.; or a small molecule that bind to the polypeptide of the present invention but do not elicit a response, so that the activity of the polypeptide is prevented.

Screening methods may also involve the use of transgenic technology and the genes set forth in Table I. The art of constructing transgenic animals is well established. For example, the genes set forth in Table I may be introduced through microinjection into the male pronucleus of fertilized oocytes, retroviral transfer into pre- or post-implantation embryos, or injection of genetically modified, such as by electroporation, embryonic stem cells into host

blastocysts. Particularly useful transgenic animals are so-called "knock-in" animals in which an animal gene is replaced by the human equivalent within the genome of that animal. Knock-in transgenic animals are useful in the drug discovery process, for target validation, where the compound is specific for the human target. Other useful transgenic animals are so-called "knock-out" animals in which the expression of the animal ortholog of a polypeptide of the present invention and encoded by an endogenous DNA sequence in a cell is partially or completely annulled. The gene knock-out may be targeted to specific cells or tissues, may occur only in certain cells or tissues as a consequence of the limitations of the technology, or may occur in all, or substantially all, cells in the animal. Transgenic animal technology also offers a whole animal expression-cloning system in which introduced genes are expressed to give large amounts of polypeptides of the present invention

Screening kits for use in the above described methods form a further aspect of the present invention. Such screening kits comprise:

- (a) a polypeptide of the present invention;
- (b) a recombinant cell expressing a polypeptide of the present invention;
- (c) a cell membrane expressing a polypeptide of the present invention; or
- (d) an antibody to a polypeptide of the present invention;

which polypeptide is preferably that set forth in the Sequence Listing.

It will be appreciated that in any such kit, (a), (b), (c) or (d) may comprise a substantial component.

### **Glossary**

The following definitions are provided to facilitate understanding of certain terms used frequently hereinbefore.

"Antibodies" as used herein includes polyclonal and monoclonal antibodies, chimeric, single chain, and humanized antibodies, as well as Fab fragments, including the products of an Fab or other immunoglobulin expression library.

"Isolated" means altered "by the hand of man" from its natural state, *i.e.*, if it occurs in nature, it has been changed or removed from its original environment, or both. For example, a polynucleotide or a polypeptide naturally present in a living organism is not "isolated," but the same polynucleotide or polypeptide separated from the coexisting materials of its natural state is "isolated", as the term is employed herein. Moreover, a polynucleotide or polypeptide that is introduced into an organism by transformation, genetic manipulation or by any other

recombinant method is "isolated" even if it is still present in said organism, which organism may be living or non-living.

"Secreted protein activity or secreted polypeptide activity" or "biological activity of the secreted protein or secreted polypeptide" refers to the metabolic or physiologic function of said secreted protein including similar activities or improved activities or these activities with decreased undesirable side-effects. Also included are antigenic and immunogenic activities of said secreted protein.

"Secreted protein gene" refers to a polynucleotide comprising any of the attached nucleotide sequences or allelic variants thereof and/or their complements.

"Polynucleotide" generally refers to any polyribonucleotide (RNA) or polydeoxribonucleotide (DNA), which may be unmodified or modified RNA or DNA. "Polynucleotides" include, without limitation, single- and double-stranded DNA, DNA that is a mixture of single- and double-stranded regions, single- and double-stranded RNA, and RNA that is mixture of single- and double-stranded regions, hybrid molecules comprising DNA and RNA that may be single-stranded or, more typically, double-stranded or a mixture of single- and double-stranded regions. In addition, "polynucleotide" refers to triple-stranded regions comprising RNA or DNA or both RNA and DNA. The term "polynucleotide" also includes DNAs or RNAs containing one or more modified bases and DNAs or RNAs with backbones modified for stability or for other reasons. "Modified" bases include, for example, tritylated bases and unusual bases such as inosine. A variety of modifications may be made to DNA and RNA; thus, "polynucleotide" embraces chemically, enzymatically or metabolically modified forms of polynucleotides as typically found in nature, as well as the chemical forms of DNA and RNA characteristic of viruses and cells. "Polynucleotide" also embraces relatively short polynucleotides, often referred to as oligonucleotides.

"Polypeptide" refers to any polypeptide comprising two or more amino acids joined to each other by peptide bonds or modified peptide bonds, i.e., peptide isosteres. "Polypeptide" refers to both short chains, commonly referred to as peptides, oligopeptides or oligomers, and to longer chains, generally referred to as proteins. Polypeptides may contain amino acids other than the 20 gene-encoded amino acids. "Polypeptides" include amino acid sequences modified either by natural processes, such as post-translational processing, or by chemical modification techniques that are well known in the art. Such modifications are well described in basic texts and in more detailed monographs, as well as in a voluminous research literature. Modifications

may occur anywhere in a polypeptide, including the peptide backbone, the amino acid side-chains and the amino or carboxyl termini. It will be appreciated that the same type of modification may be present to the same or varying degrees at several sites in a given polypeptide. Also, a given polypeptide may contain many types of modifications. Polypeptides may be branched as a result of ubiquitination, and they may be cyclic, with or without branching. Cyclic, branched and branched cyclic polypeptides may result from post-translation natural processes or may be made by synthetic methods. Modifications include acetylation, acylation, ADP-ribosylation, amidation, biotinylation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphatidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent cross-links, formation of cystine, formation of pyroglutamate, formylation, gamma-carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination (see, for instance, *Proteins - Structure and Molecular Properties*, 2nd Ed., T. E. Creighton, W. H. Freeman and Company, New York, 1993; Wold, F., *Post-translational Protein Modifications: Perspectives and Prospects*, 1-12, in *Post-translational Covalent Modification of Proteins*, B. C. Johnson, Ed., Academic Press, New York, 1983; Seifter *et al.*, "Analysis for protein modifications and nonprotein cofactors", *Meth Enzymol*, 182, 626-646, 1990, and Rattan *et al.*, "Protein Synthesis: Post-translational Modifications and Aging", *Ann NY Acad Sci*, 663, 48-62, 1992).

"Fragment" of a polypeptide sequence refers to a polypeptide sequence that is shorter than the reference sequence but that retains essentially the same biological function or activity as the reference polypeptide. "Fragment" of a polynucleotide sequence refers to a polynucleotide sequence that is shorter than the reference sequence set forth in the Sequence Listing.

"Variant" refers to a polynucleotide or polypeptide that differs from a reference polynucleotide or polypeptide, but retains the essential properties thereof. A typical variant of a polynucleotide differs in nucleotide sequence from the reference polynucleotide. Changes in the nucleotide sequence of the variant may or may not alter the amino acid sequence of a polypeptide encoded by the reference polynucleotide. Nucleotide changes may result in amino

acid substitutions, additions, deletions, fusions and truncations in the polypeptide encoded by the reference sequence, as discussed below. A typical variant of a polypeptide differs in amino acid sequence from the reference polypeptide. Generally, alterations are limited so that the sequences of the reference polypeptide and the variant are closely similar overall and, in many regions, identical. A variant and reference polypeptide may differ in amino acid sequence by one or more substitutions, insertions, deletions in any combination. A substituted or inserted amino acid residue may or may not be one encoded by the genetic code. Typical conservative substitutions include Gly, Ala; Val, Ile, Leu; Asp, Glu; Asn, Gln; Ser, Thr; Lys, Arg; and Phe and Tyr. A variant of a polynucleotide or polypeptide may be naturally occurring such as an allele, or it may be a variant that is not known to occur naturally. Non-naturally occurring variants of polynucleotides and polypeptides may be made by mutagenesis techniques or by direct synthesis. Also included as variants are polypeptides having one or more post-translational modifications, for instance glycosylation, phosphorylation, methylation, ADP ribosylation and the like. Embodiments include methylation of the N-terminal amino acid, phosphorylations of serines and threonines and modification of C-terminal glycines.

"Allele" refers to one of two or more alternative forms of a gene occurring at a given locus in the genome.

"Polymorphism" refers to a variation in nucleotide sequence (and encoded polypeptide sequence, if relevant) at a given position in the genome within a population.

"Single Nucleotide Polymorphism" (SNP) refers to the occurrence of nucleotide variability at a single nucleotide position in the genome, within a population. An SNP may occur within a gene or within intergenic regions of the genome. SNPs can be assayed using Allele Specific Amplification (ASA). For the process at least 3 primers are required. A common primer is used in reverse complement to the polymorphism being assayed. This common primer can be between 50 and 1500 bps from the polymorphic base. The other two (or more) primers are identical to each other except that the final 3' base wobbles to match one of the two (or more) alleles that make up the polymorphism. Two (or more) PCR reactions are then conducted on sample DNA, each using the common primer and one of the Allele Specific Primers.

"Splice Variant" as used herein refers to cDNA molecules produced from RNA molecules initially transcribed from the same genomic DNA sequence but which have undergone alternative RNA splicing. Alternative RNA splicing occurs when a primary RNA

transcript undergoes splicing, generally for the removal of introns, which results in the production of more than one mRNA molecule each of that may encode different amino acid sequences. The term splice variant also refers to the proteins encoded by the above cDNA molecules.

"Identity" reflects a relationship between two or more polypeptide sequences or two or more polynucleotide sequences, determined by comparing the sequences. In general, identity refers to an exact nucleotide to nucleotide or amino acid to amino acid correspondence of the two polynucleotide or two polypeptide sequences, respectively, over the length of the sequences being compared.

"% Identity" - For sequences where there is not an exact correspondence, a "% identity" may be determined. In general, the two sequences to be compared are aligned to give a maximum correlation between the sequences. This may include inserting "gaps" in either one or both sequences, to enhance the degree of alignment. A % identity may be determined over the whole length of each of the sequences being compared (so-called global alignment), that is particularly suitable for sequences of the same or very similar length, or over shorter, defined lengths (so-called local alignment), that is more suitable for sequences of unequal length.

"Similarity" is a further, more sophisticated measure of the relationship between two polypeptide sequences. In general, "similarity" means a comparison between the amino acids of two polypeptide chains, on a residue by residue basis, taking into account not only exact correspondences between a between pairs of residues, one from each of the sequences being compared (as for identity) but also, where there is not an exact correspondence, whether, on an evolutionary basis, one residue is a likely substitute for the other. This likelihood has an associated "score" from which the "% similarity" of the two sequences can then be determined.

Methods for comparing the identity and similarity of two or more sequences are well known in the art. Thus for instance, programs available in the Wisconsin Sequence Analysis Package, version 9.1 (Devereux J et al, Nucleic Acids Res, 12, 387-395, 1984, available from Genetics Computer Group, Madison, Wisconsin, USA), for example the programs BESTFIT and GAP, may be used to determine the % identity between two polynucleotides and the % identity and the % similarity between two polypeptide sequences. BESTFIT uses the "local homology" algorithm of Smith and Waterman (J Mol Biol, 147,195-197, 1981, Advances in Applied Mathematics, 2, 482-489, 1981) and finds the best single region of similarity between two sequences. BESTFIT is more suited to comparing two polynucleotide or two polypeptide

sequences that are dissimilar in length, the program assuming that the shorter sequence represents a portion of the longer. In comparison, GAP aligns two sequences, finding a "maximum similarity", according to the algorithm of Needleman and Wunsch (J Mol Biol, 48, 443-453, 1970). GAP is more suited to comparing sequences that are approximately the same length and an alignment is expected over the entire length. Preferably, the parameters "Gap Weight" and "Length Weight" used in each program are 50 and 3, for polynucleotide sequences and 12 and 4 for polypeptide sequences, respectively. Preferably, % identities and similarities are determined when the two sequences being compared are optimally aligned.

Other programs for determining identity and/or similarity between sequences are also known in the art, for instance the BLAST family of programs (Altschul S F et al, J Mol Biol, 215, 403-410, 1990, Altschul S F et al, Nucleic Acids Res., 25:389-3402, 1997, available from the National Center for Biotechnology Information (NCBI), Bethesda, Maryland, USA and accessible through the home page of the NCBI at [www.ncbi.nlm.nih.gov](http://www.ncbi.nlm.nih.gov)) and FASTA (Pearson W R, Methods in Enzymology, 183, 63-99, 1990; Pearson W R and Lipman D J, Proc Nat Acad Sci USA, 85, 2444-2448, 1988, available as part of the Wisconsin Sequence Analysis Package).

Preferably, the BLOSUM62 amino acid substitution matrix (Henikoff S and Henikoff J G, Proc. Nat. Acad Sci. USA, 89, 10915-10919, 1992) is used in polypeptide sequence comparisons including where nucleotide sequences are first translated into amino acid sequences before comparison.

Preferably, the program BESTFIT is used to determine the % identity of a query polynucleotide or a polypeptide sequence with respect to a reference polynucleotide or a polypeptide sequence, the query and the reference sequence being optimally aligned and the parameters of the program set at the default value, as hereinbefore described.

"Identity Index" is a measure of sequence relatedness which may be used to compare a candidate sequence (polynucleotide or polypeptide) and a reference sequence. Thus, for instance, a candidate polynucleotide sequence having, for example, an Identity Index of 0.95 compared to a reference polynucleotide sequence is identical to the reference sequence except that the candidate polynucleotide sequence may include on average up to five differences per each 100 nucleotides of the reference sequence. Such differences are selected from the group consisting of at least one nucleotide deletion, substitution, including transition and transversion, or insertion. These differences may occur at the 5' or 3' terminal positions of the reference polynucleotide sequence or anywhere between these terminal positions, interspersed either

individually among the nucleotides in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polynucleotide sequence having an Identity Index of 0.95 compared to a reference polynucleotide sequence, an average of up to 5 in every 100 of the nucleotides of the in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

Similarly, for a polypeptide, a candidate polypeptide sequence having, for example, an Identity Index of 0.95 compared to a reference polypeptide sequence is identical to the reference sequence except that the polypeptide sequence may include an average of up to five differences per each 100 amino acids of the reference sequence. Such differences are selected from the group consisting of at least one amino acid deletion, substitution, including conservative and non-conservative substitution, or insertion. These differences may occur at the amino- or carboxy-terminal positions of the reference polypeptide sequence or anywhere between these terminal positions, interspersed either individually among the amino acids in the reference sequence or in one or more contiguous groups within the reference sequence. In other words, to obtain a polypeptide sequence having an Identity Index of 0.95 compared to a reference polypeptide sequence, an average of up to 5 in every 100 of the amino acids in the reference sequence may be deleted, substituted or inserted, or any combination thereof, as hereinbefore described. The same applies *mutatis mutandis* for other values of the Identity Index, for instance 0.96, 0.97, 0.98 and 0.99.

The relationship between the number of nucleotide or amino acid differences and the Identity Index may be expressed in the following equation:

$$n_a \leq x_a - (x_a \bullet I),$$

in which:

$n_a$  is the number of nucleotide or amino acid differences,

$x_a$  is the total number of nucleotides or amino acids in a sequence set forth in the Sequence Listing,

I is the Identity Index,

$\bullet$  is the symbol for the multiplication operator, and

in which any non-integer product of  $x_a$  and I is rounded down to the nearest integer prior to subtracting it from  $x_a$ .



"Homolog" is a generic term used in the art to indicate a polynucleotide or polypeptide sequence possessing a high degree of sequence relatedness to a reference sequence. Such relatedness may be quantified by determining the degree of identity and/or similarity between the two sequences as hereinbefore defined. Falling within this generic term are the terms "ortholog", and "paralog". "Ortholog" refers to a polynucleotide or polypeptide that is the functional equivalent of the polynucleotide or polypeptide in another species. "Paralog" refers to a polynucleotide or polypeptide that within the same species which is functionally similar.

"Fusion protein" refers to a protein encoded by two, often unrelated, fused genes or fragments thereof. In one example, EP-A-0 464 533-A discloses fusion proteins comprising various portions of constant region of immunoglobulin molecules together with another human protein or part thereof. In many cases, employing an immunoglobulin Fc region as a part of a fusion protein is advantageous for use in therapy and diagnosis resulting in, for example, improved pharmacokinetic properties [see, *e.g.*, EP-A 0232 262]. On the other hand, for some uses it would be desirable to be able to delete the Fc part after the fusion protein has been expressed, detected and purified.

All publications and references, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference in their entirety as if each individual publication or reference were specifically and individually indicated to be incorporated by reference herein as being fully set forth. Any patent application to which this application claims priority is also incorporated by reference herein in its entirety in the manner described above for publications and references.

**Table I.**

<b>Gene Name</b>	<b>GSK Gene ID</b>	<b>Nucleic Acid SEQ ID NO's</b>	<b>Corresponding Protein SEQ ID NO's</b>
sbg123493SLITa	123493	SEQ ID NO:1	SEQ ID NO:34
sbg14936EGFa	14936	SEQ ID NO:2 SEQ ID NO:3	SEQ ID NO:35 SEQ ID NO:36
SBh80018.cyastin- related	80018	SEQ ID NO:4	SEQ ID NO:37
SBh74552.trypsinogen	74552	SEQ ID NO:5 SEQ ID NO:6	SEQ ID NO:38 SEQ ID NO:39
sbg90060IGFBP	90060	SEQ ID NO:7 SEQ ID NO:8	SEQ ID NO:40 SEQ ID NO:41
sbg97078ANGIOa	97078	SEQ ID NO:9 SEQ ID NO:10	SEQ ID NO:42 SEQ ID NO:43
sbg68091CMP	68091	SEQ ID NO:11 SEQ ID NO:12	SEQ ID NO:44 SEQ ID NO:45
sbg18525LRR	18525	SEQ ID NO:13	SEQ ID NO:46
SBh45597.trypsin inhibitor	45597	SEQ ID NO:14 SEQ ID NO:15	SEQ ID NO:47 SEQ ID NO:48
sbg34640CALa	34640	SEQ ID NO:16 SEQ ID NO:17	SEQ ID NO:49 SEQ ID NO:50
sbg14849LO	14849	SEQ ID NO:18	SEQ ID NO:51
SBh35812.CALGIZZ ARIN	35812	SEQ ID NO:19 SEQ ID NO:20	SEQ ID NO:52 SEQ ID NO:53
sbg37967ECMPa	37967	SEQ ID NO:21 SEQ ID NO:22	SEQ ID NO:54 SEQ ID NO:55
sbg15037SER	15037	SEQ ID NO:23	SEQ ID NO:56
sbg23161EGFa	23161	SEQ ID NO:24 SEQ ID NO:25	SEQ ID NO:57 SEQ ID NO:58
sbg82008TGFa	82008	SEQ ID NO:26	SEQ ID NO:59
sbg82008TGFB	82008	SEQ ID NO:27	SEQ ID NO:60
sbg27142IGBb	27142	SEQ ID NO:28 SEQ ID NO:29	SEQ ID NO:61 SEQ ID NO:62
sbg239881TAGL	239881	SEQ ID NO:30 SEQ ID NO:31	SEQ ID NO:63 SEQ ID NO:64
sbg248602CHP	248602	SEQ ID NO:32	SEQ ID NO:65
sbg219473HNKS	219473	SEQ ID NO:33	SEQ ID NO:66

Table II

Gene Name	Gene Family	Closest Polynucleotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg123493S LITa	Slit-like protein	SC:AL157714 Submitted (20-JAN-2001) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Rat slit1 protein, gi: 4585574 Brose K, Bland KS, Wang KH, Arnott D, Henzel W, Goodman CS, Tessier- Lavigne M, Kidd T. Cell 1999 Mar 19;96(6):795- 806.	Membrane- bound
sbg14936EG Fa	EGF-Like 2 family of polypeptides	GB:Z97832 Submitted (01-FEB-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse EGF-related protein SCUBE1, gi: 10998440 Submitted (08-JUN-2000) by Mammalian Genetics Unit, MRC Harwell, Chilton, Didcot, Oxon OX11 0RD, United Kingdom.	Secreted
SBh80018.c yastin- related	Cystatin- related epididymal spermatogeni c protein	GB:AL121894 Submitted (25-OCT-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse cystatin T (Zcys3), geneseq:Y96576 Patented by ZYMOGENETICS INC Patent number and and publication date: WO200031264-A2, 02- JUN-00	Secreted
SBh74552- .trypsinogen	Trypsinogen	GB:U66059 Rowen, L., Koop, B.F. and Hood, L. Science 272 (5269), 1755- 1762 (1996).	Mouse Trypsinogen, gi2358070 Rowen,L., Smit,A.F.A. and Hood,L, Submitted (20-JUL-1997) Department of Molecular Biotechnology, Box 357730 University of Washington, Seattle, Washington 98195, USA	Secreted
sbg90060- IGFBP	Insulin-like growth factor binding protein (IGFBP)	GB:AC020916 Direct submitted (12-JAN- 2000) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA	Protein PRO332, geneseq:Y13396 Patented by Genetech Inc Patent Number and publication date: WO9914328-A2, 25-Mar- 99	Secreted

Table II (cont).

Gene Name	Gene Family	Closest Polynucleotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg97078- ANGIOa	Angiotensin II/vasopressin receptor	GB:AC011476 Direct submitted (07-OCT-1999) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA.	Human hypothetical protein FLJ20510: gi:8923473. Submitted (02-Nov-2000) by Sumio Sugano, Institute of Medical Science, University of Tokyo, Department of Virology; Shirokane-dai, 4-6-1, Minato-ku, Tokyo 108-8639	Membrane-bound
sbg68091- CMP	Cartilage matrix protein	GB:AC006356 Direct Submitted (29-MAY-1999) by Genome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Parkway, St. Louis, MO 63108, USA	Human zkun5 protein, geneseq:Y52597. Patented by ZYMOGENETICS INC. Patent number and and publication date: WO9961615-A1, 02-Dec-99	Secreted
sbg18525- LRR	Leucine-rich repeat (LLR)	GB:AC016030 Direct submitted (19-NOV-1999) by Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA	Human KIAA0416 protein, gi:7662102. Ishikawa,K., Nagase,T., Nakajima,D., Seki,N., Ohira,M., Miyajima,N., Tanaka,A., Kotani,H., Nomura,N. and Ohara,O. 1997. DNA Res. 4:307-313.	Membrane-bound
SBh45597- .trypsin inhibitor	Rab subfamily of Ras-like GTPase	SC:Z84479 Submitted (16-OCT-1997) by Sanger Centre, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SA, UK.	Human RAS like GTPASE, gi:3036779. Submitted (16-OCT-1997) Sanger Centre, Wellcome Trust Genome Campus, Hinxton, Cambridgeshire, CB10 1SA, UK.	Cytosolic
sbg34640- CALa	Calgizzarin (endothelial monocyte-activating polypeptide)	GB:AC006483 Sulston,J.E. and Waterston,R Genome Res. 8 (11), 1097-1108 (1998)	Human calgizzarin, gi:1710818. Tanaka,M., Adzuma,K., Iwami,M., Yoshimoto,K., Monden,Y. and Itakura,M. Cancer Lett. 89 (2), 195-200 (1995).	Cytosolic

Table II (cont).

Gene Name	Gene Family	Closest Polynucleotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg14849LO	Lysyl oxidase-like	GB:AC005033 Direct Submitted (12-JUN-1998) by Genome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Parkway, St. Louis, MO 63108, USA.	Mouse lysyl oxidase-related protein 2, gi:7305239. Jang,W., Hua,A., Spilson,S.V., Miller,W., Roe,B.A. and Meisler,M.H., 1999, Genome Res. 9 : 53-61.	Secreted
SBh35812-CALGIZ-ZARIN	Calgizzarin (endothelial monocyte-activating polypeptide)	GB:AL133399 Submitted (08-FEB-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse calgizzarin, gi:1710819. Submitted (27-NOV-1995) Keith A. Houck, Biomolecular Research, Sphinx Pharmaceuticals Corp., 4615 University Dr., Durham, NC 27707, USA	Cytosolic
sbg37967-ECMPa	Extracellular matrix protein 2	JENA:X57A-X51X57A-X51 found at Jena Genome Sequencing Center	Human extracellular matrix protein 2, gi:4557543. Nishiu,J., Tanaka,T. and Nakamura,Y. Genomics 52, 378-381 (1998)	Secreted
sbg15037-SER	Serine protease	GB:AC005570 Direct submitted (01-SEP-1998) Center for Human Genome Studies, DOE Joint Genome Institute, Los Alamos National Laboratory, MS M888, Los Alamos, NM 87545, USA.	A long isoform of human HELA2 protein, W77297 Patented by Amrad Operations Pty Ltd. Patent number and and publication date: WO9836054-A1, 20-AUG-98	Secreted
sbg23161-EGFa	Extracellular/epidermal growth factor	GB:Z99756, GB:Z82214 Submitted (08-DEC-1999) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK.	Mouse EGF-related protein SCUBE1 gi:10998440. Grimmond,S., Larder,R., Van Hateren,N., Siggers,P., Hulsebos,T.J.M., Arkell,R. and Greenfield, A. Genomics 70 (1), 74-81 (2000)	Secreted
sbg82008-TGFa,b	TGF beta (transforming growth factor beta)	GB:AC008940.frag1. Submitted (03-AUG-1999) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA	A novel isolated and purified growth factor (GF), Y16714. Patented by UNIV WASHINGTON. Patent number and and publication date: WO9914235, 25-MAR-99	Secreted

Table II (cont).

Gene Name	Gene Family	Closest Polynucleotide by homology	Closest Polypeptide by homology	Cell Localization (by homology)
sbg27142-IGBb	Immunoglobulin superfamily	GB:AC011846: Submitted (15-OCT-1999) Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA GB:AC068507: Submitted (03-MAY-2000) Whitehead Institute/MIT Center for Genome Research, 320 Charles Street, Cambridge, MA 02141, USA	Mouse cell adhesion molecule, gi:11862939. Submitted (11-DEC-2000) Junya Toguchida, Kyoto University, Institute for Frontier Medical Sciences; 53 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto, Kyoto 606-8507, Japan	Secreted
sbg239881-TAGL	Tag7-like family protein	GB:AC011492 Direct submitted (07-OCT-1999) by Production Sequencing Facility, DOE Joint Genome Institute, 2800 Mitchell Drive, Walnut Creek, CA 94598, USA.	Mouse TAGL-alpha protein, gi: 10946624. Submitted (11-MAY-1999) Laboratory of Cancer Molecular Genetics, Institute of Gene Biology, Russian Academy of Sciences, 34/5 Vavilov Street, Moscow 117334, Russia	Secreted
sbg248602-CHP	Zinc Carboxypeptidase	GB:AL035460 Direct submitted (20-MAR-2000) by Sanger Centre, Hinxton, Cambridgeshire, CB10 1SA, UK	Mouse metallocarboxypeptidase CPX-1, AAD15985. Lei, Y., Xin, X., Morgan, D., Pinter, J.E. and Fricker, L.D, 1999, DNA Cell Biol. 18:175-185.	Secreted
sbg219473-HNKS	HNK-sulfotransferase	GB:AP001087 Direct submitted (25-JAN-2000) by the Institute of Physical and Chemical Research (RIKEN), Genomic Sciences Center (GSC); Kitasato Univ., 1-15-1 Kitasato, Sagamihara, Kanagawa 228-8555, Japan.	Human GalNAc 4-sulfotransferase, gi:11990885. Habuchi, O. and Okuda, T. J. Biol. Chem. 275 (51), 40605-40613 (2000)	Membrane-bound

Table III.

Gene Name	Uses	Associated Diseases
sbg123493-SLITa	An embodiment of the invention may be the use of sbg123493-SLITa, a secreted protein, to bind Robo receptors and have an evolutionarily conserved role in repulsive axon guidance and may be useful for the prevention and treatment of diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, muscular system and colon. sbg123493-SLITa may also be used in the treatment of pineal tumors and alleviation of precocious puberty. Close homologs of sbg123493-SLITa are rat protein-Slit protein and pineal gland specific gene-1 protein.	Diseases in spinal cord, thyroid gland, ovary, prostate, renal gland, small intestine, heart, trachea, thymus, lymph node, muscular system and colon, pineal tumors and alleviation of precocious puberty
sbg14936-EGFa	An embodiment of the invention is the use of sbg14936-EGFa, a secreted protein, to treat colorectal carcinomas, and peptic ulcer healing. The closest homologue to sbg14936-EGFa is high-molecular-weight proteins with multiple EGF-like motifs. Polypeptides with EGF-like and/or cadherin-like repeats have been used to stimulate the growth of various epidermal and epithelial tissues <i>in vivo</i> and <i>in vitro</i> and of some fibroblasts in cell culture.	Neurodegenerative disorders, trauma, natural blinding, colorectal carcinomas and peptic ulcer healing
SBh80018-cyastin-related	An embodiment of the invention is the use of SBh80018-cyastin-related to treat or prevent tissue damage associated with brain hemorrhage.	Autoimmune disorder, hematopoietic disorder, wound healing disorder, viral and bacterial infection, cancer, neurological disorder, brain haemorrhage, tissue damage, inflammation, and protection and remodeling of the eye
SBh74552-trypsinogen	An embodiment of the invention is the use of SBh74552-trypsinogen to treat clot formation induced by myocardial infarction and reocclusion following angioplasty or pulmonary thromboembolism. Close homologues to of SBh74552-trypsinogen are used to treat clot formation and for treating associated gastrointestinal and haematopoietic disorders.	Autoimmune disorder, hematopoietic disorder, wound healing disorder, viral and bacterial infection, cancer, clot formation in myocardial infarction, reocclusion following angioplasty or pulmonary thromboembolism, gastrointestinal disorders

Table III (cont).

Gene Name	Uses	Associated Diseases
sbg90060-IGFBP	An embodiment of the invention is the use of sbg90060-IGFBP, in the treatment of a wide range of disease states including cancer, diabetes, vascular disease, asthma, and growth disorders. Close homologs of sbg90060-IGFBP are Insulin-like growth factor (IGF) binding proteins (IGFBP). IGFBP when occupied by IGF, combines with an acid-labile glycoprotein subunit (ALS) to form a high molecular weight complex. The IGFBPs regulate somatic growth and cellular proliferation both in vivo and in vitro. The IGFBPs also appear to have emerging roles in the mechanisms underlying human cancer. Future research on its physiology may have advancements in the treatment of a wide range of disease states including cancer, diabetes, vascular disease, asthma, and growth disorders (Wetterau LA, Moore MG, Lee KW, Shim ML, Cohen P, 1999, Mol Genet Metab 68:161-81).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, diabetes, vascular disease, asthma, and growth disorders
sbg97078-ANGIOa	An embodiment of the invention is the use of sbg97078-ANGIOa, in treating hypertension, heart disease, and kidney disease, related to unbalanced levels of angiotensin II/vasopressin receptors. A close homolog of sbg97078-ANGIOa is angiotensin II/vasopressin receptors. Angiotensin II/vasopressin receptors couple to adenylate cyclase and responds with equal sensitivity to Ang II and AVP. Ang II receptors respond to the neurotransmitter angiotensin II whilst AVP receptors respond to arginine vasopressin. Vasopressin receptor mediates many central and peripheral actions of vasopressin, including intracellular calcium mobilization. Thus the proteins, antibodies, agonists and antagonists can be used for treating, e.g. hypertension, heart disease, and kidney disease, related to unbalanced levels of angiotensin II/vasopressin receptor (Howl J, Wheatley M, 1995 Gen Pharmacol 26:1143-52; Grazzini E, Boccara G, Joubert D, Trueba M, Durroux T, Guillon G, Gallo-Payet N, Chouinard L, Payet MD, Serradeil Le Gal C, 1998 Adv Exp Med Biol 449:325-34).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, hypertension, heart disease, and kidney disease
sbg68091-CMP	An embodiment of the invention is the use of sbg68091-CMP, in repairing damaged cartilage in joints, such as in osteoarthritis and rheumatoid arthritis. A close homolog of sbg68091-CMP is Matrilin-1. The matrilin family shares a common structure made up of von Willebrand factor A domains, epidermal growth factor-like domains and a coiled coil alpha-helical module (Deak F, Wagener R, Kiss I, Paulsson M, 1999. Matrix Biol 18:55-64). Matrilin-1, cartilage matrix protein (CMP), is a major component of the extracellular matrix of nonarticular cartilage, and it binds to collagen.	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, rheumatoid arthritis, and osteoarthritis.



Table III (cont).

Gene Name	Uses	Associated Diseases
sbg18525-LRR	An embodiment of the invention is the use of sbg18525-LRR a member of the leucine-rich repeat protein family, in immunization , protein-protein interactions, such as cell adhesion or receptor-ligand binding and neuronal LRR may be an important component of the pathophysiological response to brain injury. Close homologs of sbg18525-LRR are leucine-rich repeat (LRR) proteins such as connectin, slit, chaoptin, and toll. These proteins have important roles in neuronal development and the adult nervous system as cell adhesion molecules (Taguchi A, Wanaka A, Mori T, Matsumoto K, Imai Y, Tagaki T, Tohyama M, 1996, Brain Res Mol Brain Res;35:31-4). At least one LRR was shown to be specifically expressed on B cells, suggesting its role in immunization (Miyake K, Yamashita Y, Ogata M, Sudo T, Kimoto M, 1995, J Immunol 154:3333-40). Some studies have shown that brain injury can cause over expression of neuronal LRR, suggesting that neuronal LRR may be an important component of the pathophysiological response to brain injury (Ishii N, Wanaka A, Tohyama M, 1996, Brain Res Mol Brain Res 40: 148-52)..	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, gastrointestinal ulceration, and diseases in spinal cord, thyroid gland, heart, trachea, thymus, lymph node, muscular system, and nervous system
SBh45597-trypsin inhibitor	An embodiment of the invention is the use of SBh45597-trypsin inhibitor in vesicle targeting. The Rabs are a subfamily within the large group of small GTP-binding proteins and have been showed to play a role in vesicle targeting. Like RAS, they cycle between active GTP-bound and inactive GDP-bound forms with both transitions to require additional factors: GTPase-activating proteins (GAPs) and guanine nucleotide exchange factors (GEFs). The GDP-bound form is also a target for a GDI (GDP dissociation inhibitor), a slightly-misnamed but remarkable protein which extracts the GDP-Rab (including its very hydrophobic isoprenoid groups) from the membrane, allowing it to return via the cytosol to its membrane of origin. (Armstrong J. Int J Biochem Cell Biol 2000 Mar;32(3):303-7).	Acute respiratory disease, AIDs, allergy, atherosclerosis, cancer, biabetes, cerebral neoplasm, immune disorder, imflasmatory disorder, rheumatoid arthritis, viral infection.
sbg34640-CALa	An embodiment of the invention is the use of sbg34640-CALa, a secreted protein, in the diagnosis and treatment of cancer. Close homologues to sbg34640-CALa are S100 calcium-binding protein A11 (calgizzarin) and other EF-hand calcium binding proteins and more specifically to s-100/CABP like proteins. S100 calcium-binding protein A11 (calgizzarin) binds two calcium ions per molecule with an affinity similar to that of the s-100 proteins. s-100/CABP like proteins are useful in diagnosis and treatment of cancer. (Fan, Y., Leung, D., Houck, K.A., Yan, S., Kao, J. Calgizzarin (endothelial monocyte-activating polypeptide ((EMAP) Submitted JAN-1996 to the EMBL/GenBank/DDBJ databases. ACCESSION NO: P50543.).	Infections, cancers, autoimmune disorders, wound healing disorder and hematopoietic disorder

Table III (cont).

Gene Name	Uses	Associated Diseases
sbgl4849LO	An embodiment of the invention is the use of sbgl4849LO in the biogenesis of connective tissue matrices by crosslinking the extracellular matrix proteins, collagen and elastin or in the treatment of osteoporotic bone. A close homologue of sbgl4849LO is lysyl oxidase (LO). LO is a cuproenzyme that plays a critical role in the biogenesis of connective tissue matrices by crosslinking the extracellular matrix proteins, collagen and elastin. Levels of LO increase in many fibrotic diseases, while expression of the enzyme is decreased in some diseases related to impaired copper metabolism. Transforming growth factor-beta, platelet-derived growth factor, angiotensin II, retinoic acid, fibroblast growth factor, and altered serum conditions can affect LO expression. It has also become increasingly evident that LO may have other important biological functions (Smith-Mungo LI, and Kagan HM, 1998, Matrix Biol 16:387-98). In mineralizing tissues, a relatively low level of lysyl hydroxylation results in low levels of hydroxyllysyl pyridinoline, and the occurrence of the largely bone specific lysyl pyridinoline and pyrrolic cross-links (Knott L, and Bailey AJ, 1998, Bone 22:181-7).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorder, inflammation, fibrotic diseases, and metabolic bone diseases
SBh35812-CALGIZ-ZARIN	An embodiment of the invention is the use of SBh35812-CALGIZ-ZARIN to activate host response mechanisms. Close homologues of SBh35812-CALGIZ-ZARIN are cytokines and S-100 PROTEINS.	Autoimmune disorder, hematopoietic disorder, wound healing disorder, viral and bacterial infection, cancer, melanoma cancer, cerebral dysfunction
sbgl37967-ECMPa	An embodiment of the invention is the use of sbgl37967-ECMPa, a secreted protein, in wound healing and treatment of inflammatory diseases. A close homologue to sbgl37967-ECMPa is extracellular matrix protein 2 (pECM2). pECM2 expressed predominantly in adipose and female-specific tissues and its chromosomal localization to 9q22.3 and participates in protein-protein interactions and/or cell-ECM recognition processes (Nishiu, J., Tanaka, T. and Nakamura, Y. 1998. Genomics 52, 378-381).	Cancer, autoimmune disease, inflammatory diseases, wound healing and hematopoietic disorder
sbgl5037-SER	An embodiment of the invention is the use of sbgl5037-SER in the diagnosis of testicular tumors. sbgl5037-SER is a membrane-type serine protease which shows a trypsin-like cleavage activity. A close homologue to sbgl5037-SER is testisin, a new human serine proteinase, which is abundantly expressed only in the testis and is lost in testicular tumors. These findings about testisin demonstrate a new cell surface serine proteinase, loss of which may have a role in the progression of testicular tumors of germ cell origin. (Hooper JD, Nicol DL, Dickinson JL, Eyre HJ, Scarman AL, Normyle JF, Stuttgart MA, Douglas ML, Loveland KA, Sutherland GR, and Antalis TM, 1999, Cancer Res 59:3199-205).	Cancer, including testicular tumors, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders, and inflammation

Table III (cont).

Gene Name	Uses	Associated Diseases
sbg23161-EGFa	An embodiment of the invention is the use of sbg23161-EGFa, a secreted protein, in regulating vascular smooth muscle cell proliferation, e.g. for enhancing neurological functions or treating neoplasia and other disorders. A close homologue to sbg23161-EGFa is human extracellular/epidermal growth factor-like protein(EEGF). This EEGF protein is useful for regulating vascular smooth muscle cell proliferation, e.g. for enhancing neurological functions or treating neoplasia and other disorders (LI HS and OLSEN H, New isolated extracellular/epidermal growth factor, Accession Number W79739, HUMAN GENOME SCI INC).	Cancer, autoimmune disorders, wound healing disorders, infections, and hemotopoietic disorders
sbg82008-TGFa,b	An embodiment of the invention is the use of sbg82008-TGFa,b in growth control and hence the etiology of cancer, cell differentiation and development. sbg82008-TGFa,b contains the Prosite consensus pattern (PDOC00223) for TGF beta family members. Close homologues of sbg82008-TGFa,b are TGF-beta proteins. TGF-beta proteins are known to be involved in growth control and hence the etiology of cancer ( <i>Anticancer Res</i> 1999 Nov-Dec;19(6A):4791-807), cell differentiation and development. A TGF-beta signaling pathway constitutes a tumor suppressor path ( <i>Cytokine Growth Factor Rev</i> 2000 Apr 1;11(1-2):159-168).	Cancer (eg., lymphoma, leukemia, renal cell carcinoma, melanoma, lung cancer), infection (viral disease, (eg hepatitis A and C), parasitic disease, bacterial disease), inflammation, autoimmune disorder (eg multiple sclerosis, Type I diabetes), infertility, miscarriage, hematopoietic disorder, wound healing disorder, inflammatory diseases, inflammatory bowel disease, cystic fibrosis, immune deficiency, thrombocytopenia, chronic obstructive pulmonary disease
sbg27142-IGBb	An embodiment of the invention is the use of sbg27142-IGBb in the diagnosis and/or treatment of cancer and autoimmune disorders of the nervous system. A close homologue to sbg27142-IGBb is the mouse cell adhesion molecule (gi:11862939) that has been associated with transformation of osteoblasts and the mouse gene Punc that is expressed predominantly in the developing nervous system (Salbaum, J.M. 1998 Mech. Dev. 71 (1-2), 201-204).	Cancer, infection diseases, autoimmune disorder, wound healing disorder and hematopoietic disorder
sbg239881-TAGL	An embodiment of the invention is the use of sbg239881-TAGL to inhibit tumor growth and induce apoptosis and/or may also be useful as probes for gene mapping and detection of tag7 gene expression. Close homologues to sbg239881-TAGL and its promoter region are genes of the tumor necrosis factor (TNF). The tag7 coding sequences are also useful as probes for gene mapping and detection of tag7 gene expression (Kiselev SL, Kustikova OS, Korobko EV, Prokhortchouk EB, Kabishev AA, Lukanidin EM, Georgiev GP, 1998, J Biol Chem 273:18633-9).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders

**Table III (cont).**

Gene Name	Uses	Associated Diseases
sbg248602- CHP	Due to the carboxypeptidase activity required for processing of various neuropeptides and hormones, an embodiment of the invention is the use of sbg248602-CHP in treatments of neurodegenerative disorders and developmental abnormalities. Close homologues to sbg248602-CHP are peptidases that catalyze the removal of c-terminal basic amino acid residues, and is involved in processing of neuropeptides and hormones in secretory vesicles (Manser E, Fernandez D, Loo L, Goh PY, Monfries C, Hall C, and Lim L, 1990, <i>Biochem J</i> 267:517-25). Some enzymes from this family have been isolated in multiple forms from both soluble and membrane-bound compartments, and are demonstrated to co-secrete with peptides from pancreatic and adrenal cells. Single mRNA species have been shown to yield multiple forms of similar peptidases (Manser E, Fernandez D, and Lim L, 1991, <i>Biochem J</i> 280:695-701).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders, inflammation, neurodegenerative disorders, and developmental abnormalities
sbg219473- HNKS	An embodiment of the invention may be the use of sbg219473-HNKS in the development of the nervous system, and may also be involved in the preferential reinnervation of muscle nerves by motor axons after lesion. Close homologues to sbg219473-HNKS are sulfotransferases. Sulfotransferase is considered to be the key enzyme in the biosynthesis of the HNK-1 carbohydrate epitope, which is expressed on several neural adhesion glycoproteins and as a glycolipid, and is involved in cell interactions (Bakker, H., Friedmann, I., Oka, S., Kawasaki, T., Nifant'ev, N., Schachner, M., and Mantei, N., 1997, <i>J. Biol. Chem.</i> 272:29942-29946). The HNK-1 epitope is spatially and temporally regulated during the development of the nervous system. The biological function of the HNK-1 sulfotransferase may be related to the development of the nervous system, and also may be involved in the preferential reinnervation of muscle nerves by motor axons after lesion (Jungalwala FB, 1994, <i>Neurochem Res</i> 19:945-57).	Cancer, infection, autoimmune disorder, hematopoietic disorder, wound healing disorders, inflammation, and peripheral neuropathies

**Table IV. Quantitative, Tissue-specific mRNA expression detected using SybrMan**

Quantitative, tissue-specific, mRNA expression patterns of the genes were measured using SYBR-Green Quantitative PCR (Applied Biosystems, Foster City, CA; see Schmittgen T.D. et al., *Analytical Biochemistry* 285:194-204, 2000) and human cDNAs prepared from various human tissues. Gene-specific PCR primers were designed using the first nucleic acid sequence listed in the Sequence List for each gene. Results are presented as the number of copies of each specific gene's mRNA detected in 1ng mRNA pool from each tissue. Two replicate mRNA measurements were made from each tissue RNA.

Table IV Cont

Gene Name	Tissue-Specific mRNA Expression (copies per ng mRNA; avg. $\pm$ range for 2 data points per tissue)									
	Brain	Heart	Lung	Liver	Kidney	Skeletal muscle	Intestine	Spleen/lymph	Placenta	Testis
sbg123493-SLITa	9 $\pm$ 3	70 $\pm$ 31	13 $\pm$ 3	-1 $\pm$ 1	41 $\pm$ 16	132 $\pm$ 21	6 $\pm$ 2	5 $\pm$ 10	9 $\pm$ 4	959 $\pm$ 80
sbg14936-EGFa	516 $\pm$ 3 4	2424 $\pm$ 72	550 $\pm$ 56	129 $\pm$ 7	1825 $\pm$ 6	1503 $\pm$ 168	218 $\pm$ 26	423 $\pm$ 4	629 $\pm$ 39	1765 $\pm$ 40
SBh80018-.cyastin-related	1 $\pm$ 0	2 $\pm$ 1	0 $\pm$ 0	-7 $\pm$ 4	2 $\pm$ 3	6 $\pm$ 4	-3 $\pm$ 3	2 $\pm$ 0	0 $\pm$ 1	5258 $\pm$ 259
SBh74552-.trypsinogen	-1 $\pm$ 1	7 $\pm$ 1	9 $\pm$ 1	-10 $\pm$ 1	1 $\pm$ 3	4 $\pm$ 1	3 $\pm$ 0	10 $\pm$ 3	5 $\pm$ 0	5159 $\pm$ 907
sbg90060-IGFBP	366 $\pm$ 17	659 $\pm$ 36	784 $\pm$ 64	53 $\pm$ 7	1035 $\pm$ 189	119 $\pm$ 15	109 $\pm$ 4	531 $\pm$ 12	582 $\pm$ 8	207 $\pm$ 13
sbg97078-ANGIOa	15 $\pm$ 1	16 $\pm$ 7	58 $\pm$ 3	-6 $\pm$ 1	18 $\pm$ 1	4 $\pm$ 1	37 $\pm$ 2	91 $\pm$ 5	244 $\pm$ 3	688 $\pm$ 18
sbg68091-CMP	1360 $\pm$ 30	3596 $\pm$ 59	1846 $\pm$ 271	248 $\pm$ 18	2596 $\pm$ 146	2351 $\pm$ 5	1646 $\pm$ 112	486 $\pm$ 4	3228 $\pm$ 327	3204 $\pm$ 42
sbg18525-LRR	4290 $\pm$ 157	367 $\pm$ 6	47 $\pm$ 4	7 $\pm$ 0	263 $\pm$ 10	69 $\pm$ 7	401 $\pm$ 62	39 $\pm$ 3	119 $\pm$ 17	307 $\pm$ 1
SBh45597-.trypsin inhibitor	59 $\pm$ 12	58 $\pm$ 7	44 $\pm$ 1	22 $\pm$ 1	106 $\pm$ 21	45 $\pm$ 6	36 $\pm$ 6	49 $\pm$ 16	57 $\pm$ 9	219 $\pm$ 55
sbg34640-CALa	3006 $\pm$ 11	30001 $\pm$ 197	98054 $\pm$ 1290	4166 $\pm$ 228	39196 $\pm$ 1674	9611 $\pm$ 323	31417 $\pm$ 619	70617 $\pm$ 2786	203542 $\pm$ 4017	20011 $\pm$ 2747
sbg14849-LO	508 $\pm$ 23	862 $\pm$ 13	631 $\pm$ 8	51 $\pm$ 5	251 $\pm$ 24	125 $\pm$ 12	348 $\pm$ 38	662 $\pm$ 17	1404 $\pm$ 138	721 $\pm$ 69
SBh35812.-CALGIZ-ZARIN	345 $\pm$ 1	20 $\pm$ 1	11 $\pm$ 1	-3 $\pm$ 7	45 $\pm$ 1	8 $\pm$ 7	5 $\pm$ 2	15 $\pm$ 4	20 $\pm$ 5	136 $\pm$ 20
sbg37967-ECMPa	72 $\pm$ 5	26 $\pm$ 10	24 $\pm$ 8	3 $\pm$ 9	45 $\pm$ 0	18 $\pm$ 1	4 $\pm$ 3	34 $\pm$ 10	593 $\pm$ 62	57 $\pm$ 5
sbg15037-SER	291 $\pm$ 9	256 $\pm$ 24	284 $\pm$ 18	302 $\pm$ 7	312 $\pm$ 6	298 $\pm$ 8	264 $\pm$ 17	256 $\pm$ 4	277 $\pm$ 14	316 $\pm$ 55
sbg23161-EGFa	150 $\pm$ 1	142 $\pm$ 9	2063 $\pm$ 68	348 $\pm$ 20	1184 $\pm$ 80	79 $\pm$ 13	809 $\pm$ 41	1276 $\pm$ 17	831 $\pm$ 22	2635 $\pm$ 156

Table IV Cont

Gene Name	Tissue-Specific mRNA Expression (copies per ng mRNA; avg. $\pm$ range for 2 data points per tissue)									
	Brain	Heart	Lung	Liver	Kidney	Skeletal muscle	Intestine	Spleen /lymph	Placenta	Testis
sbg82008-TGFa,b	1542 $\pm 96$	651 $\pm 49$	858 $\pm 37$	555 $\pm 30$	818 $\pm 248$	829 $\pm 47$	321 $\pm 28$	721 $\pm 108$	1037 $\pm 51$	670 $\pm 110$
sbg2714-2IGBb	526 $\pm 3$ 7	505 $\pm 8$	115 $\pm 5$	-6 $\pm 9$	91 $\pm 3$	3783 $\pm$ 80	173 $\pm 1$	211 $\pm 3$ 7	5218 $\pm$ 240	354 $\pm 3$ 9
sbg23988-1TAGL	3 $\pm 1$	2 $\pm 0$	6 $\pm 1$	2816 $\pm 28$	6 $\pm 1$	0 $\pm 0$	3 $\pm 1$	-2 $\pm 5$	4 $\pm 0$	780 $\pm 20$
sbg248602-CHP	134 $\pm 10$	989 $\pm 16$	539 $\pm 3$	3 $\pm 5$	1335 $\pm 16$	80 $\pm 17$	385 $\pm 18$	730 $\pm 43$	15644 $\pm 309$	921 $\pm 9$
sbg219473-HNKS	175 $\pm 32$	1075 $\pm 81$	2522 $\pm 91$	473 $\pm 35$	453 $\pm 57$	74 $\pm 18$	98 $\pm 1$	1121 $\pm 12$	10 $\pm 6$	2813 $\pm 148$

Table V. Additional diseases based on mRNA expression in specific tissues

Tissue Expression	Additional Diseases
Brain	Neurological and psychiatric diseases, including Alzheimers, parasupranuclear palsey, Huntington's disease, myotonic dystrophy, anorexia, depression, schizophrenia, headache, amnesias, anxiety disorders, sleep disorders, multiple sclerosis
Heart	Cardiovascular diseases, including congestive heart failure, dilated cardiomyopathy, cardiac arrhythmias, Hodgson's Disease, myocardial infarction, cardiac arrhythmias
Lung	Respiratory diseases, including asthma, Chronic Obstructive Pulmonary Disease, cystic fibrosis, acute bronchitis, adult respiratory distress syndrome
Liver	Dyslipidemia, hypercholesterolemia, hypertriglyceridemia, cirrhosis, hepatic encephalopathy, fatty hepatocirrhosis, viral and nonviral hepatitis, Type II Diabetes Mellitis, impaired glucose tolerance
Kidney	Renal diseases, including acute and chronic renal failure, acute tubular necrosis, cystinuria, Fanconi's Syndrome, glomerulonephritis, renal cell carcinoma, renovascular hypertension
Skeletal muscle	Eulenburg's Disease, hypoglycemia, obesity, tendinitis, periodic paralyses, malignant hyperthermia, paramyotonia congenita, myotonia congenita
Intestine	Gastrointestinal diseases, including Myotonia congenita, Ileus, Intestinal Obstruction, Tropical Sprue, Pseudomembranous Enterocolitis
Spleen/lymph	Lymphangiectasia, hypersplenism, angiomas, ankylosing spondylitis, Hodgkin's Disease, macroglobulinemia, malignant lymphomas, rheumatoid arthritis
Placenta	Choriocarcinoma, hydatidiform mole, placenta previa
Testis	Testicular cancer, male reproductive diseases, including low testosterone and male infertility
Pancreas	Diabetic ketoacidosis, Type 1 & 2 diabetes, obesity, impaired glucose tolerance

**What is claimed is:**

1. An isolated polypeptide selected from the group consisting of:
  - (a) an isolated polypeptide encoded by a polynucleotide comprising a sequence set forth in Table I;
  - (b) an isolated polypeptide comprising a polypeptide sequence set forth in Table I; and
  - (c) a polypeptide sequence of a gene set forth in Table I.
2. An isolated polynucleotide selected from the group consisting of:
  - (a) an isolated polynucleotide comprising a polynucleotide sequence set forth in Table I;
  - (b) an isolated polynucleotide of a gene set forth in Table I;
  - (c) an isolated polynucleotide comprising a polynucleotide sequence encoding a polypeptide set forth in Table I;
  - (d) an isolated polynucleotide encoding a polypeptide set forth in Table I;
  - (e) a polynucleotide which is an RNA equivalent of the polynucleotide of (a) to (d);or a polynucleotide sequence complementary to said isolated polynucleotide.
3. An expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 when said expression vector is present in a compatible host cell.
4. A process for producing a recombinant host cell which comprises the step of introducing an expression vector comprising a polynucleotide capable of producing a polypeptide of claim 1 into a cell such that the host cell, under appropriate culture conditions, produces said polypeptide.
5. A recombinant host cell produced by the process of claim 4.
6. A membrane of a recombinant host cell of claim 5 expressing said polypeptide.
7. A process for producing a polypeptide which comprises culturing a host cell of claim 5 under conditions sufficient for the production of said polypeptide and recovering said polypeptide from the culture.

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&lt;213&gt; Homo sapiens

&lt;400&gt; 9

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&lt;213&gt; Homo sapiens

&lt;400&gt; 10

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&lt;213&gt; Homo sapiens

&lt;400&gt; 11

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&lt;213&gt; Homo sapiens

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&lt;211&gt; 1482

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 13

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;211&gt; 861

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 15

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 19

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&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 20

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&lt;211&gt; 1932

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

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&lt;210&gt; 22

&lt;211&gt; 1962

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 22

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&lt;211&gt; 918

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 23

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&lt;211&gt; 1164

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 24

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&lt;211&gt; 3753

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 29

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&lt;210&gt; 30

&lt;211&gt; 1905

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 30

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&lt;210&gt; 31

&lt;211&gt; 1731

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 31

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&lt;210&gt; 32

&lt;211&gt; 2205

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 32

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&lt;210&gt; 33

&lt;211&gt; 1077

&lt;212&gt; DNA

&lt;213&gt; Homo sapiens

&lt;400&gt; 33

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 <211> 256  
 <212> PRT  
 <213> Homo sapiens

<400> 34  
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 Gln Ala Gln Glu Val Ile Cys Thr Gly Lys Gln Leu Thr Glu Tyr Pro  
 35 40 45  
 Leu Asp Ile Pro Leu Asn Thr Arg Arg Leu Phe Leu Asn Glu Asn Arg  
 50 55 60  
 Ile Thr Ser Leu Pro Ala Met His Leu Gly Leu Leu Ser Asp Leu Val  
 65 70 75 80  
 Tyr Leu Asp Cys Gln Asn Asn Arg Ile Arg Glu Val Met Asp Tyr Thr  
 85 90 95  
 Phe Ile Gly Val Phe Lys Leu Ile Tyr Leu Asp Leu Ser Ser Asn Asn  
 100 105 110  
 Leu Thr Ser Ile Ser Pro Phe Thr Phe Ser Val Leu Ser Asn Leu Val  
 115 120 125  
 Gln Leu Asn Ile Ala Asn Asn Pro His Leu Leu Ser Leu His Lys Phe  
 130 135 140  
 Thr Phe Ala Asn Thr Thr Ser Leu Arg Tyr Leu Asp Leu Arg Asn Thr  
 145 150 155 160  
 Gly Leu Gln Thr Leu Asp Ser Ala Ala Leu Tyr His Leu Thr Thr Leu  
 165 170 175  
 Glu Thr Leu Phe Leu Ser Gly Asn Pro Trp Lys Cys Asn Cys Ser Phe  
 180 185 190  
 Leu Asp Phe Ala Ile Phe Leu Ile Val Phe His Met Asp Pro Ser Gly  
 195 200 205  
 Glu Gly Leu Ile Gly Cys Gly Glu Glu Asp Val Ile Glu Val Ala Pro  
 210 215 220  
 Glu Lys Val Asn Ser Lys Asp Gly Gln Asn Gly Arg Lys Ser Trp Val  
 225 230 235 240  
 Lys Leu Ile Glu Cys Ile Leu Ile Thr Leu Gln Gly Pro Pro Leu Gly  
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<210> 35  
 <211> 897  
 <212> PRT  
 <213> Homo sapiens

<400> 35  
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 35 40 45  
 Thr Pro Arg Ser Tyr Lys Cys Ile Cys Lys Ser Gly Tyr Thr Gly Asp  
 50 55 60  
 Gly Lys His Cys Lys Asp Val Asp Glu Cys Glu Arg Glu Asp Asn Ala  
 65 70 75 80  
 Gly Cys Val His Asp Cys Val Asn Ile Pro Gly Asn Tyr Arg Cys Thr

20/60

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Val	Asp	Glu	Cys	Ala	Glu	Gly	Asn	Gly	Gly	Cys	Gln	Gln	Ser	Cys	Val		
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Asn	Met	Met	Gly	Ser	Tyr	Glu	Cys	His	Cys	Arg	Glu	Gly	Phe	Phe	Leu		
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Ser	Asp	Asn	Gln	His	Thr	Cys	Ile	Gln	Arg	Pro	Glu	Glu	Gly	Met	Asn		
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Cys	Met	Asn	Lys	Asn	His	Gly	Cys	Ala	His	Ile	Cys	Arg	Glu	Thr	Pro		
			165						170					175			
Lys	Gly	Gly	Ile	Ala	Cys	Glu	Cys	Arg	Pro	Gly	Phe	Glu	Leu	Thr	Lys		
			180					185					190				
Asn	Gln	Arg	Asp	Cys	Lys	Cys	Glu	Ile	Ile	Gly	Met	Ala	Val	Thr	Cys		
		195					200					205					
Asn	Tyr	Gly	Asn	Gly	Gly	Cys	Gln	His	Thr	Cys	Asp	Asp	Thr	Glu	Gln		
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Gly	Pro	Arg	Cys	Gly	Cys	His	Ile	Lys	Phe	Val	Leu	His	Thr	Asp	Gly		
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Lys	Thr	Cys	Ile	Glu	Thr	Cys	Ala	Val	Asn	Asn	Gly	Gly	Cys	Asp	Ser		
			245						250					255			
Lys	Cys	His	Asp	Ala	Ala	Thr	Gly	Val	His	Cys	Thr	Cys	Pro	Val	Gly		
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Phe	Met	Leu	Gln	Pro	Asp	Arg	Lys	Thr	Cys	Lys	Asp	Ile	Asp	Glu	Cys		
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Arg	Leu	Asn	Asn	Gly	Gly	Cys	Asp	His	Ile	Cys	Arg	Asn	Thr	Val	Gly		
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Ser	Phe	Glu	Cys	Ser	Cys	Lys	Lys	Gly	Tyr	Lys	Leu	Leu	Ile	Asn	Glu		
305				310						315					320		
Arg	Asn	Cys	Gln	Asp	Ile	Asp	Glu	Cys	Ser	Phe	Asp	Arg	Thr	Cys	Asp		
			325						330					335			
His	Ile	Cys	Val	Asn	Thr	Pro	Gly	Ser	Phe	Gln	Cys	Leu	Cys	His	Arg		
			340					345					350				
Gly	Tyr	Leu	Leu	Tyr	Gly	Ile	Thr	His	Cys	Gly	Asp	Val	Asp	Glu	Cys		
		355					360					365					
Ser	Ile	Asn	Arg	Gly	Gly	Cys	Arg	Phe	Gly	Cys	Ile	Asn	Thr	Pro	Gly		
		370				375					380						
Ser	Tyr	Gln	Cys	Thr	Cys	Pro	Ala	Gly	Gln	Gly	Arg	Leu	His	Trp	Asn		
385				390						395					400		
Gly	Lys	Asp	Cys	Thr	Glu	Pro</											

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 565 570 575  
 Pro Pro Ala Ser Cys Gly Leu Pro Cys Leu Arg Gln Arg Met Glu Arg  
 580 585 590  
 Arg Leu Lys Gly Ser Leu Lys Met Leu Arg Lys Ser Ile Asn Gln Asp  
 595 600 605  
 Arg Phe Leu Leu Arg Leu Ala Gly Leu Asp Tyr Glu Leu Ala His Lys  
 610 615 620  
 Pro Gly Leu Val Ala Gly Glu Arg Ala Glu Pro Met Glu Ser Cys Arg  
 625 630 635 640  
 Pro Gly Gln His Arg Ala Gly Thr Lys Cys Val Gln Cys Ser Pro Gly  
 645 650 655  
 His Tyr Tyr Asn Thr Ser Ile His Arg Cys Ile Arg Cys Ala Met Gly  
 660 665 670  
 Ser Tyr Gln Pro Asp Phe Arg Gln Asn Phe Cys Ser Arg Cys Pro Gly  
 675 680 685  
 Asn Thr Ser Thr Asp Phe Asp Gly Ser Thr Ser Val Ala Gln Cys Lys  
 690 695 700  
 Asn Arg Gln Cys Gly Gly Glu Leu Gly Glu Phe Thr Gly Tyr Ile Glu  
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 Ser Pro Asn Tyr Pro Gly Asn Tyr Pro Ala Gly Val Glu Cys Ile Trp  
 725 730 735  
 Asn Ile Asn Pro Pro Pro Lys Arg Lys Ile Leu Ile Val Val Pro Glu  
 740 745 750  
 Ile Phe Leu Pro Ser Glu Asp Glu Cys Gly Asp Val Leu Val Met Arg  
 755 760 765  
 Lys Asn Ser Ser Pro Ser Ser Ile Thr Thr Tyr Glu Thr Cys Gln Thr  
 770 775 780  
 Tyr Glu Arg Pro Ile Ala Phe Thr Ala Arg Ser Arg Lys Leu Trp Ile  
 785 790 795 800  
 Asn Phe Lys Thr Ser Glu Ala Asn Ser Ala Arg Gly Phe Gln Ile Pro  
 805 810 815  
 Tyr Val Thr Tyr Asp Glu Asp Tyr Glu Gln Leu Val Glu Asp Ile Val  
 820 825 830  
 Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn His Gln Glu Ile Leu Lys  
 835 840 845  
 Asp Lys Lys Leu Ile Lys Ala Phe Phe Glu Val Leu Ala His Pro Gln  
 850 855 860  
 Asn Tyr Phe Lys Tyr Thr Glu Lys His Lys Glu Met Leu Pro Lys Ser  
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 885 890 895  
 Lys

<210> 36  
 <211> 993  
 <212> PRT  
 <213> Homo sapiens

<400> 36  
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 20 25 30  
 Cys Val Glu Gly Thr Asp Asn Cys His Ile Asp Ala Ile Cys Gln Asn  
 35 40 45  
 Thr Pro Arg Ser Tyr Lys Cys Ile Cys Lys Ser Gly Tyr Thr Gly Asp  
 50 55 60

22/60

Gly Lys His Cys Lys Asp Val Asp Glu Cys Glu Arg Glu Asp Asn Ala  
 65 70 75 80  
 Gly Cys Val His Asp Cys Val Asn Ile Pro Gly Asn Tyr Arg Cys Thr  
 85 90 95  
 Cys Tyr Asp Gly Phe His Leu Ala His Asp Gly His Asn Cys Leu Asp  
 100 105 110  
 Val Asp Glu Cys Ala Glu Gly Asn Gly Gly Cys Gln Gln Ser Cys Val  
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 Asn Met Met Gly Ser Tyr Glu Cys His Cys Arg Glu Gly Phe Phe Leu  
 130 135 140  
 Ser Asp Asn Gln His Thr Cys Ile Gln Arg Pro Glu Glu Gly Met Asn  
 145 150 155 160  
 Cys Met Asn Lys Asn His Gly Cys Ala His Ile Cys Arg Glu Thr Pro  
 165 170 175  
 Lys Gly Gly Ile Ala Cys Glu Cys Arg Pro Gly Phe Glu Leu Thr Lys  
 180 185 190  
 Asn Gln Arg Asp Cys Lys Leu Thr Cys Asn Tyr Gly Asn Gly Gly Cys  
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 Gln His Thr Cys Asp Asp Thr Glu Gln Gly Pro Arg Cys Gly Cys His  
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 Gly Val His Cys Thr Cys Pro Val Gly Phe Met Leu Gln Pro Asp Arg  
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 290 295 300  
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 Glu Cys Ser Phe Asp Arg Thr Cys Asp His Ile Cys Val Asn Thr Pro  
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 Gly Ser Phe Gln Cys Leu Cys His Arg Gly Tyr Leu Leu Tyr Gly Ile  
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 355 360 365  
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 420 425 430  
 Ala Arg Phe Leu Pro Glu Ser Glu Asn Gly Phe Thr Val Ser Cys Gly  
 435 440 445  
 Thr Pro Ser Pro Arg Ala Ala Pro Ala Arg Ala Gly His Asn Gly Asn  
 450 455 460  
 Ser Thr Asn Ser Asn His Cys His Glu Ala Ala Val Leu Ser Ile Lys  
 465 470 475 480  
 Gln Arg Ala Ser Phe Lys Ile Lys Asp Ala Lys Cys Arg Leu His Leu  
 485 490 495  
 Arg Asn Lys Gly Lys Thr Glu Glu Ala Gly Arg Ile Thr Gly Pro Gly  
 500 505 510  
 Gly Ala Pro Cys Ser Glu Cys Gln Val Thr Phe Ile His Leu Lys Cys  
 515 520 525  
 Asp Ser Ser Arg Lys Gly Lys Gly Arg Arg Ala Arg Thr Pro Pro Gly

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Glu Glu Thr Thr Ala Ser Cys Gly Leu Pro Cys Leu Arg Gln Arg Met				560
	565		570	
Glu Arg Arg Leu Lys Gly Ser Leu Lys Met Leu Arg Lys Ser Ile Asn				575
	580		585	
Gln Asp Arg Phe Leu Leu Arg Leu Ala Gly Leu Asp Tyr Glu Leu Ala				590
	595		600	
His Lys Pro Gly Leu Val Ala Gly Glu Arg Ala Glu Pro Met Glu Ser				605
	610		615	
Cys Arg Pro Gly Gln His Arg Ala Gly Thr Lys Cys Val Ser Cys Pro				620
625		630		635
Gln Gly Thr Tyr Tyr His Gly Gln Thr Glu Gln Cys Val Pro Cys Pro				640
	645		650	
Ala Gly Thr Phe Gln Glu Arg Glu Gly Gln Leu Ser Cys Asp Leu Cys				655
	660		665	
Pro Gly Ser Asp Ala His Gly Pro Leu Gly Ala Thr Asn Val Thr Thr				670
	675		680	
Cys Ala Gly Gln Cys Pro Pro Gly Gln His Ser Val Asp Gly Phe Lys				685
	690		695	
Pro Cys Gln Pro Cys Pro Arg Gly Thr Tyr Gln Pro Glu Ala Gly Arg				700
705		710		715
Thr Leu Cys Phe Pro Cys Gly Gly Gly Leu Thr Thr Lys His Glu Gly				720
	725		730	
Ala Ile Ser Phe Gln Asp Cys Asp Thr Lys Val Gln Cys Ser Pro Gly				735
	740		745	
His Tyr Tyr Asn Thr Ser Ile His Arg Cys Ile Arg Cys Ala Met Gly				750
	755		760	
Ser Tyr Gln Pro Asp Phe Arg Gln Asn Phe Cys Ser Arg Cys Pro Gly				765
	770		775	
Asn Thr Ser Thr Asp Phe Asp Gly Ser Thr Ser Val Ala Gln Cys Lys				780
785		790		795
Asn Arg Gln Cys Gly Gly Glu Leu Gly Glu Phe Thr Gly Tyr Ile Glu				800
	805		810	
Ser Pro Asn Tyr Pro Gly Asn Tyr Pro Ala Gly Val Glu Cys Ile Trp				815
	820		825	
Asn Ile Asn Pro Pro Pro Lys Arg Lys Ile Leu Ile Val Val Pro Glu				830
	835		840	
Ile Phe Leu Pro Ser Glu Asp Glu Cys Gly Asp Val Leu Val Met Arg				845
	850		855	
Lys Asn Ser Ser Pro Ser Ser Ile Thr Thr Tyr Glu Thr Cys Gln Thr				860
865		870		875
Tyr Glu Arg Pro Ile Ala Phe Thr Ala Arg Ser Arg Lys Leu Trp Ile				880
	885		890	
Asn Phe Lys Thr Ser Glu Ala Asn Ser Ala Arg Gly Phe Gln Ile Pro				895
	900		905	
Tyr Val Thr Tyr Asp Glu Asp Tyr Glu Gln Leu Val Glu Asp Ile Val				910
	915		920	
Arg Asp Gly Arg Leu Tyr Ala Ser Glu Asn His Gln Glu Ile Leu Lys				925
	930		935	
Asp Lys Lys Leu Ile Lys Ala Phe Phe Glu Val Leu Ala His Pro Gln				940
945		950		955
Asn Tyr Phe Lys Tyr Thr Glu Lys His Lys Glu Met Leu Pro Lys Ser				960
	965		970	
Phe Ile Lys Leu Leu Arg Ser Lys Val Ser Ser Phe Leu Arg Pro Tyr				975
	980		985	
				990

Lys

<210> 37  
 <211> 138  
 <212> PRT  
 <213> Homo sapiens

<400> 37

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Met Val Arg Leu Cys Gln Ala Leu Leu Leu Leu Val Ala Thr Val Ala
 1          5          10          15
Leu Ala Ser Arg Arg Phe Gln Ala Trp Gly Ser Thr Lys Val Val Arg
          20          25          30
Thr Phe Gln Asp Ile Pro Gln Asn Tyr Val Tyr Val Gln Gln Ala Leu
          35          40          45
Trp Phe Ala Met Lys Glu Tyr Asn Lys Ala Ser Phe Ser Ile Thr Ser
 50          55          60
Ser Ala Leu Gly Lys Glu Tyr Lys Leu Lys Val Thr Asp Ser Leu Glu
 65          70          75          80
Tyr Tyr Ile Glu Val Lys Ile Ala Arg Thr Ile Cys Lys Lys Ile Ser
          85          90          95
Glu Asp Glu Asn Cys Ala Phe Gln Glu Asp Pro Lys Met Gln Lys Val
          100          105          110
Val Phe Cys Thr Phe Ile Val Ala Ser Lys Pro Trp Lys Phe Glu Leu
          115          120          125
Thr Met Leu Lys Lys Gln Cys Lys Asp Met
 130          135

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<210> 38  
 <211> 241  
 <212> PRT  
 <213> Homo sapiens

<400> 38

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Met Lys Phe Ile Leu Leu Trp Ala Leu Leu Asn Leu Thr Val Ala Leu
 1          5          10          15
Ala Phe Asn Pro Asp Tyr Thr Val Ser Ser Thr Pro Pro Tyr Leu Val
          20          25          30
Tyr Leu Lys Ser Asp Tyr Leu Pro Cys Ala Gly Val Leu Ile His Pro
          35          40          45
Leu Trp Val Ile Thr Ala Ala His Cys Asn Leu Pro Lys Leu Arg Val
          50          55          60
Ile Leu Gly Val Thr Ile Pro Ala Asp Ser Asn Glu Lys His Leu Gln
 65          70          75          80
Val Ile Gly Tyr Glu Lys Met Ile His His Pro His Phe Ser Val Thr
          85          90          95
Ser Ile Asp His Asp Ile Met Leu Ile Lys Leu Lys Thr Glu Ala Glu
          100          105          110
Leu Asn Asp Tyr Val Lys Leu Ala Asn Leu Pro Tyr Gln Thr Ile Ser
          115          120          125
Glu Asn Thr Met Cys Ser Val Ser Thr Trp Ser Tyr Asn Val Cys Asp
          130          135          140
Ile Tyr Lys Glu Pro Asp Ser Leu Gln Thr Val Asn Ile Ser Val Ile
 145          150          155          160
Ser Lys Pro Gln Cys Arg Asp Ala Tyr Lys Thr Tyr Asn Ile Thr Glu
          165          170          175
Asn Met Leu Cys Val Gly Ile Val Pro Gly Arg Arg Gln Pro Cys Lys
          180          185          190
Glu Val Ser Ala Ala Pro Ala Ile Cys Asn Gly Met Leu Gln Gly Ile
          195          200          205
Leu Ser Phe Ala Asp Gly Cys Val Leu Arg Ala Asp Val Gly Ile Tyr

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25/60



210	215	220
Ala Lys Ile Phe Tyr Tyr Ile Pro Trp Ile Glu Asn Val Ile Gln Asn		
225	230	235
Asn		240

<210> 39  
 <211> 243  
 <212> PRT  
 <213> Homo sapiens

<400> 39

Met Thr Glu Lys Ser Trp Asn Phe Leu Ser Met Leu Leu Phe Pro Val	
1 5 10 15	
Ala Leu Ala Phe Asn Pro Asp Tyr Thr Val Ser Ser Thr Pro Pro Tyr	
20 25 30	
Leu Val Tyr Leu Lys Ser Asp Tyr Leu Pro Cys Ala Gly Val Leu Ile	
35 40 45	
His Pro Leu Trp Val Ile Thr Ala Ala His Cys Asn Leu Pro Lys Leu	
50 55 60	
Arg Val Ile Leu Gly Val Thr Ile Pro Ala Asp Ser Asn Glu Lys His	
65 70 75 80	
Leu Gln Val Ile Gly Tyr Glu Lys Met Ile His His Pro His Phe Ser	
85 90 95	
Val Thr Ser Ile Asp His Asp Ile Met Leu Ile Lys Leu Lys Thr Glu	
100 105 110	
Ala Glu Leu Asn Asp Tyr Val Lys Leu Ala Asn Leu Pro Tyr Gln Thr	
115 120 125	
Ile Ser Glu Asn Thr Met Cys Ser Val Ser Thr Trp Ser Tyr Asn Val	
130 135 140	
Cys Asp Ile Tyr Lys Glu Pro Asp Ser Leu Gln Thr Val Asn Ile Ser	
145 150 155 160	
Val Ile Ser Lys Pro Gln Cys Arg Asp Ala Tyr Lys Thr Tyr Asn Ile	
165 170 175	
Thr Glu Asn Met Leu Cys Val Gly Ile Val Pro Gly Arg Arg Gln Pro	
180 185 190	
Cys Lys Glu Val Ser Ala Ala Pro Ala Ile Cys Asn Gly Met Leu Gln	
195 200 205	
Gly Ile Leu Ser Phe Ala Asp Gly Cys Val Leu Arg Ala Asp Val Gly	
210 215 220	
Ile Tyr Ala Lys Ile Phe Tyr Tyr Ile Pro Trp Ile Glu Asn Val Ile	
225 230 235 240	
Gln Asn Asn	

<210> 40  
 <211> 483  
 <212> PRT  
 <213> Homo sapiens

<400> 40

Met Tyr Pro Gly Trp Pro Gly Gln Gly Met Trp Ala Ser Gly Gln Arg	
1 5 10 15	
Leu Pro Asp Glu Ala Phe Glu Ser Leu Thr Gln Leu Gln His Leu Cys	
20 25 30	
Val Ala His Asn Lys Leu Ser Val Ala Pro Gln Phe Leu Pro Arg Ser	
35 40 45	
Leu Arg Val Ala Asp Leu Ala Ala Asn Gln Val Met Glu Ile Phe Pro	
50 55 60	

Leu Thr Phe Gly Glu Lys Pro Ala Leu Arg Ser Val Tyr Leu His Asn  
 65 70 75 80  
 Asn Gln Leu Ser Asn Ala Gly Leu Pro Pro Asp Ala Phe Arg Gly Ser  
 85 90 95  
 Glu Ala Ile Ala Thr Leu Ser Leu Ser Asn Asn Gln Leu Ser Tyr Leu  
 100 105 110  
 Pro Pro Ser Leu Pro Pro Ser Leu Glu Arg Leu His Leu Gln Asn Asn  
 115 120 125  
 Leu Ile Ser Lys Val Pro Arg Gly Ala Leu Ser Arg Gln Thr Gln Leu  
 130 135 140  
 Arg Glu Leu Tyr Leu Gln His Asn Gln Leu Thr Asp Ser Gly Leu Asp  
 145 150 155 160  
 Ala Thr Thr Phe Ser Lys Leu His Ser Leu Glu Tyr Leu Asp Leu Ser  
 165 170 175  
 His Asn Gln Leu Thr Thr Val Pro Ala Gly Leu Pro Arg Thr Leu Ala  
 180 185 190  
 Ile Leu His Leu Gly Arg Asn Arg Ile Arg Gln Val Glu Ala Ala Arg  
 195 200 205  
 Leu His Gly Ala Arg Gly Leu Arg Tyr Leu Leu Leu Gln His Asn Gln  
 210 215 220  
 Leu Gly Ser Ser Gly Leu Pro Ala Gly Ala Leu Arg Pro Leu Arg Gly  
 225 230 235 240  
 Leu His Thr Leu His Leu Tyr Gly Asn Gly Leu Asp Arg Val Pro Pro  
 245 250 255  
 Ala Leu Pro Arg Arg Leu Arg Ala Leu Val Leu Pro His Asn His Val  
 260 265 270  
 Ala Ala Leu Gly Ala Arg Asp Leu Val Ala Thr Pro Gly Leu Thr Glu  
 275 280 285  
 Leu Asn Leu Ala Tyr Asn Arg Leu Ala Ser Ala Arg Val His His Arg  
 290 295 300  
 Ala Phe Arg Arg Leu Arg Ala Leu Arg Ser Leu Asp Leu Ala Gly Asn  
 305 310 315 320  
 Gln Leu Thr Arg Leu Pro Met Gly Leu Pro Thr Gly Leu Arg Thr Leu  
 325 330 335  
 Gln Leu Gln Arg Asn Gln Leu Arg Met Leu Glu Pro Glu Pro Leu Ala  
 340 345 350  
 Gly Leu Asp Gln Leu Arg Glu Leu Ser Leu Ala His Asn Arg Leu Arg  
 355 360 365  
 Val Gly Asp Ile Gly Pro Gly Thr Trp His Glu Leu Gln Ala Leu Gln  
 370 375 380  
 Met Leu Asp Leu Ser His Asn Glu Leu Ser Phe Val Pro Pro Asp Leu  
 385 390 395 400  
 Pro Glu Ala Leu Glu Leu His Leu Glu Gly Asn Arg Ile Gly His  
 405 410 415  
 Val Gly Pro Glu Ala Phe Leu Ser Thr Pro Arg Leu Arg Ala Leu Phe  
 420 425 430  
 Leu Arg Ala Asn Arg Leu His Met Thr Ser Ile Ala Ala Glu Ala Phe  
 435 440 445  
 Leu Gly Leu Pro Asn Leu Arg Val Val Asp Thr Ala Gly Asn Pro Glu  
 450 455 460  
 Gln Val Leu Ile Arg Leu Pro Pro Thr Thr Pro Arg Gly Pro Arg Ala  
 465 470 475 480  
 Gly Gly Pro

<210> 41  
 <211> 605  
 <212> PRT  
 <213> Homo sapiens

<400> 41

Met	Ala	Glu	Ser	Gly	Leu	Ala	Met	Glu	Gly	Met	Leu	Gln	Ser	Pro	Trp
1				5					10					15	
Arg	Pro	Cys	Ala	Gln	Pro	Gly	Asp	Thr	Leu	Thr	Leu	Pro	Pro	Pro	Gln
			20					25					30		
Trp	Pro	Ser	Leu	Leu	Leu	Leu	Leu	Leu	Leu	Pro	Gly	Pro	Pro	Pro	Val
		35					40					45			
Ala	Gly	Leu	Glu	Asp	Ala	Ala	Phe	Pro	His	Leu	Gly	Glu	Ser	Leu	Gln
	50					55					60				
Pro	Leu	Pro	Arg	Ala	Cys	Pro	Leu	Arg	Cys	Ser	Cys	Pro	Arg	Val	Asp
65					70					75					80
Thr	Val	Asp	Cys	Asp	Gly	Leu	Asp	Leu	Arg	Val	Phe	Pro	Asp	Asn	Ile
				85					90					95	
Thr	Arg	Ala	Ala	Gln	His	Leu	Ser	Leu	Gln	Asn	Asn	Gln	Leu	Gln	Glu
			100					105					110		
Leu	Pro	Tyr	Asn	Glu	Leu	Ser	Arg	Leu	Ser	Gly	Leu	Arg	Thr	Leu	Asn
		115					120					125			
Leu	His	Asn	Asn	Leu	Ile	Ser	Ser	Glu	Gly	Leu	Pro	Asp	Glu	Ala	Phe
	130					135					140				
Glu	Ser	Leu	Thr	Gln	Leu	Gln	His	Leu	Cys	Val	Ala	His	Asn	Lys	Leu
145					150					155					160
Ser	Val	Ala	Pro	Gln	Phe	Leu	Pro	Arg	Ser	Leu	Arg	Val	Ala	Asp	Leu
				165					170					175	
Ala	Ala	Asn	Gln	Val	Met	Glu	Ile	Phe	Pro	Leu	Thr	Phe	Gly	Glu	Lys
			180					185					190		
Pro	Ala	Leu	Arg	Ser	Val	Tyr	Leu	His	Asn	Asn	Gln	Leu	Ser	Asn	Ala
		195					200					205			
Gly	Leu	Pro	Pro	Asp	Ala	Phe	Arg	Gly	Ser	Glu	Ala	Ile	Ala	Thr	Leu
	210				215						220				
Ser	Leu	Ser	Asn	Asn	Gln	Leu	Ser	Tyr	Leu	Pro	Pro	Ser	Leu	Pro	Pro
225				230						235					240
Ser	Leu	Glu	Arg	Leu	His	Leu	Gln	Asn	Asn	Leu	Ile	Ser	Lys	Val	Pro
				245					250					255	
Arg	Gly	Ala	Leu	Ser	Arg	Gln	Thr	Gln	Leu	Arg	Glu	Leu	Tyr	Leu	Gln
			260					265					270		
His	Asn	Gln	Leu	Thr	Asp	Ser	Gly	Leu	Asp	Ala	Thr	Thr	Phe	Ser	Lys
		275					280					285			
Leu	His	Ser	Leu	Glu	Tyr	Leu	Asp	Leu	Ser	His	Asn	Gln	Leu	Thr	Thr
	290					295					300				
Val	Pro	Ala	Gly	Leu	Pro	Arg	Thr	Leu	Ala	Ile	Leu	His	Leu	Gly	Arg
305					310					315					320
Asn	Arg	Ile	Arg	Gln	Val	Glu	Ala	Ala	Arg	Leu	His	Gly	Ala	Arg	Gly
				325					330					335	
Leu	Arg	Tyr	Leu	Leu	Leu	Gln	His	Asn	Gln	Leu	Gly	Ser	Ser	Gly	Leu
			340					345					350		
Pro	Ala	Gly	Ala	Leu	Arg	Pro	Leu	Arg	Gly	Leu	His	Thr	Leu	His	Leu
		355					360					365			
Tyr	Gly	Asn	Gly	Leu	Asp	Arg	Val	Pro	Pro	Ala	Leu	Pro	Arg	Arg	Leu
	370					375					380				
Arg	Ala	Leu	Val	Leu	Pro	His	Asn	His	Val	Ala	Ala	Leu	Gly	Ala	Arg
385					390					395					400
Asp	Leu	Val	Ala	Thr	Pro	Gly	Leu	Thr	Glu	Leu	Asn	Leu	Ala	Tyr	Asn
			405						410					415	
Arg	Leu	Ala	Ser	Ala	Arg	Val	His	His	Arg	Ala	Phe	Arg	Arg	Leu	Arg
			420					425					430		
Ala	Leu	Arg	Ser	Leu	Asp	Leu	Ala	Gly	Asn	Gln	Leu	Thr	Arg	Leu	Pro
		435					440					445			
Met	Gly	Leu	Pro	Thr	Gly	Leu	Arg	Thr	Leu	Gln	Leu	Gln	Arg	Asn	Gln

450		455		460
Leu Arg Met Leu Glu Pro Glu Pro Leu Ala Gly Leu Asp Gln Leu Arg				
465		470		475
Glu Leu Ser Leu Ala His Asn Arg Leu Arg Val Gly Asp Ile Gly Pro				480
	485		490	495
Gly Thr Trp His Glu Leu Gln Ala Leu Gln Met Leu Asp Leu Ser His				
	500		505	510
Asn Glu Leu Ser Phe Val Pro Pro Asp Leu Pro Glu Ala Leu Glu Glu				
	515		520	525
Leu His Leu Glu Gly Asn Arg Ile Gly His Val Gly Pro Glu Ala Phe				
	530		535	540
Leu Ser Thr Pro Arg Leu Arg Ala Leu Phe Leu Arg Ala Asn Arg Leu				
	545		550	555
His Met Thr Ser Ile Ala Ala Glu Ala Phe Leu Gly Leu Pro Asn Leu				
	565		570	575
Arg Val Val Asp Thr Ala Gly Asn Pro Glu Gln Val Leu Ile Arg Leu				
	580		585	590
Pro Pro Thr Thr Pro Arg Gly Pro Arg Ala Gly Gly Pro				
	595		600	605

<210> 42  
 <211> 1049  
 <212> PRT  
 <213> Homo sapiens

<400> 42
Met Val Thr Arg Glu Leu Phe Phe Leu Phe Ser Pro Gln Phe Phe Ser
1 5 10 15
Leu Asn Leu Arg Ser His Thr Arg Ser Thr Met Thr Ser Pro Gln Leu
20 25 30
Glu Trp Thr Leu Gln Thr Leu Leu Glu Gln Leu Asn Glu Asp Glu Leu
35 40 45
Lys Ser Phe Lys Ser Leu Leu Trp Ala Phe Pro Leu Glu Asp Val Leu
50 55 60
Gln Lys Thr Pro Trp Ser Glu Val Glu Glu Ala Asp Gly Lys Lys Leu
65 70 75 80
Ala Glu Ile Leu Val Asn Thr Ser Ser Glu Asn Trp Ile Arg Asn Ala
85 90 95
Thr Val Asn Ile Leu Glu Glu Met Asn Leu Thr Glu Leu Cys Lys Met
100 105 110
Ala Lys Ala Glu Met Met Glu Asp Gly Gln Val Gln Glu Ile Asp Asn
115 120 125
Pro Glu Leu Gly Asp Ala Glu Glu Asp Ser Glu Leu Ala Lys Pro Gly
130 135 140
Glu Lys Glu Gly Trp Arg Asn Ser Met Glu Lys Gln Ser Leu Val Trp
145 150 155 160
Lys Asn Thr Phe Trp Gln Gly Asp Ile Asp Asn Phe His Asp Asp Val
165 170 175
Thr Leu Arg Asn Gln Arg Phe Ile Pro Phe Leu Asn Pro Arg Thr Pro
180 185 190
Arg Lys Leu Thr Pro Tyr Thr Val Val Leu His Gly Pro Ala Gly Val
195 200 205
Gly Lys Thr Thr Leu Ala Lys Lys Cys Met Leu Asp Trp Thr Asp Cys
210 215 220
Asn Leu Ser Pro Thr Leu Arg Tyr Ala Phe Tyr Leu Ser Cys Lys Glu
225 230 235 240
Leu Ser Arg Met Gly Pro Cys Ser Phe Ala Glu Leu Ile Ser Lys Asp
245 250 255
Trp Pro Glu Leu Gln Asp Asp Ile Pro Ser Ile Leu Ala Gln Ala Gln

29/60

		260				265			270
Arg	Ile	Leu	Phe	Val	Val	Asp	Gly	Leu	Asp
		275					280		
Gly	Ala	Leu	Ile	Gln	Asp	Ile	Cys	Gly	Asp
		290				295			
Val	Pro	Val	Leu	Leu	Gly	Ser	Leu	Leu	Lys
		305			310				
Ala	Ala	Leu	Leu	Val	Thr	Thr	Arg	Pro	Arg
				325				330	
Leu	Leu	Ala	Gln	Gln	Pro	Ile	Tyr	Val	Arg
			340					345	
Glu	Asp	Arg	Arg	Ala	Tyr	Phe	Leu	Arg	His
		355					360		
Ala	Met	Arg	Ala	Phe	Glu	Leu	Met	Arg	Ser
		370				375			
Leu	Gly	Ser	Ala	Pro	Ala	Val	Cys	Trp	Ile
		385			390				
Leu	Gln	Met	Glu	Lys	Gly	Glu	Asp	Pro	Val
			405					410	
Thr	Gly	Leu	Phe	Leu	Arg	Phe	Leu	Cys	Ser
			420					425	
Gln	Leu	Arg	Gly	Ala	Leu	Arg	Thr	Leu	Ser
		435					440		
Leu	Trp	Ala	Gln	Met	Ser	Val	Phe	His	Arg
		450				455			
Gly	Val	Gln	Glu	Ser	Asp	Leu	Arg	Leu	Phe
		465			470			475	
Arg	Gln	Asp	Arg	Val	Ser	Lys	Gly	Cys	Tyr
			485					490	
Phe	Gln	Gln	Phe	Leu	Thr	Ala	Leu	Phe	Tyr
			500					505	
Gly	Glu	Asp	Arg	Asp	Gly	His	Ala	Trp	Asp
		515					520		
Leu	Leu	Ser	Gly	Glu	Glu	Arg	Leu	Lys	Asn
		530				535			
Gly	His	Phe	Leu	Phe	Gly	Leu	Ala	Asn	Glu
		545			550				
Glu	Ala	Thr	Phe	Gly	Cys	Arg	Met	Ser	Pro
			565					570	
Leu	Gln	Cys	Lys	Ala	His	Leu	His	Ala	Asn
			580					585	
Asp	Leu	Lys	Glu	Val	Leu	Gly	Cys	Leu	Tyr
		595					600		
Leu	Ala	Lys	Val	Val	Val	Ala	Pro	Phe	Lys
		610				615			
Thr	Asn	Thr	Ser	Glu	Val	Met	His	Cys	Ser
		625			630				
Gln	Asp	Leu	Gln	Lys	Leu	Ser	Leu	Gln	Val
			645					650	
Glu	Asn	Tyr	Met	Asp	Phe	Glu	Leu	Asp	Ile
			660					665	
Ser	Asn	Leu	Lys	Phe	Leu	Glu	Val	Lys	Gln
		675						680	
Ser	Val	Arg	Ile	Leu	Cys	Asp	His	Val	Thr
		690				695			
Gln	Lys	Val	Glu	Ile	Lys	Asn	Val	Thr	Pro
		705			710				
Phe	Cys	Leu	Ala	Phe	Ile	Gly	Lys	Lys	Thr
				725					730

Ala Gly His Ile Glu Trp Glu Arg Thr Met Met Leu Met Leu Cys Asp  
 740 745 750  
 Leu Leu Arg Asn His Lys Cys Asn Leu Gln Tyr Leu Arg Leu Gly Gly  
 755 760 765  
 His Cys Ala Thr Pro Glu Gln Trp Ala Glu Phe Phe Tyr Val Leu Lys  
 770 775 780  
 Ala Asn Gln Ser Leu Lys His Leu Arg Leu Ser Ala Asn Val Leu Leu  
 785 790 795 800  
 Asp Glu Gly Ala Met Leu Leu Tyr Lys Thr Met Thr Arg Pro Lys His  
 805 810 815  
 Phe Leu Gln Met Leu Ser Leu Glu Asn Cys Arg Leu Thr Glu Ala Ser  
 820 825 830  
 Cys Lys Asp Leu Ala Ala Val Leu Val Val Ser Lys Lys Leu Thr His  
 835 840 845  
 Leu Cys Leu Ala Lys Asn Pro Ile Gly Asp Thr Gly Val Lys Phe Leu  
 850 855 860  
 Cys Glu Gly Leu Ser Tyr Pro Asp Cys Lys Leu Gln Thr Leu Val Leu  
 865 870 875 880  
 Val Ser Cys Ser Ala Thr Thr Gln Gln Trp Ala Asp Leu Ser Leu Ala  
 885 890 895  
 Leu Glu Val Asn Gln Ser Leu Thr Cys Val Asn Leu Ser Asp Asn Glu  
 900 905 910  
 Leu Leu Asp Glu Gly Ala Lys Leu Leu Tyr Thr Thr Leu Arg His Pro  
 915 920 925  
 Lys Cys Phe Leu Gln Arg Leu Ser Leu Glu Asn Cys His Leu Thr Glu  
 930 935 940  
 Ala Asn Cys Lys Asp Leu Ala Ala Val Leu Val Val Ser Arg Glu Leu  
 945 950 955 960  
 Thr His Leu Cys Leu Ala Lys Asn Pro Ile Gly Asn Thr Gly Val Lys  
 965 970 975  
 Phe Leu Cys Glu Gly Leu Arg Tyr Pro Glu Cys Lys Leu Gln Thr Leu  
 980 985 990  
 Val Leu Gln Gln Cys Ser Ile Thr Lys Leu Gly Cys Arg Tyr Leu Ser  
 995 1000 1005  
 Glu Ala Leu Gln Glu Ala Cys Ser Leu Thr Asn Leu Asp Leu Ser Ile  
 1010 1015 1020  
 Asn Gln Ile Ala Arg Gly Leu Trp Ile Leu Cys Gln Ala Leu Glu Asn  
 1025 1030 1035 1040  
 Pro Asn Cys Asn Leu Lys His Leu Arg  
 1045

<210> 43  
 <211> 1062  
 <212> PRT  
 <213> Homo sapiens

<400> 43  
 Met Val Ser Ser Ala Gln Met Gly Phe Asn Leu Gln Ala Leu Leu Glu  
 1 5 10 15  
 Gln Leu Ser Gln Asp Glu Leu Ser Lys Phe Lys Tyr Leu Ile Thr Thr  
 20 25 30  
 Phe Ser Leu Ala His Glu Leu Gln Lys Ile Pro His Lys Glu Val Asp  
 35 40 45  
 Lys Ala Asp Gly Lys Gln Leu Val Glu Ile Leu Thr Thr His Cys Asp  
 50 55 60  
 Ser Tyr Trp Val Glu Met Ala Ser Leu Gln Val Phe Glu Lys Met His  
 65 70 75 80  
 Arg Met Asp Leu Ser Glu Arg Ala Lys Asp Glu Val Arg Glu Ala Ala  
 85 90 95

31/60

Leu Lys Ser Phe Asn Lys Arg Lys Pro Leu Ser Leu Gly Ile Thr Arg  
 100 105 110  
 Lys Glu Arg Pro Pro Leu Asp Val Asp Glu Met Leu Glu Arg Phe Lys  
 115 120 125  
 Thr Glu Ala Gln Ala Phe Thr Glu Thr Lys Gly Asn Val Ile Cys Leu  
 130 135 140  
 Gly Lys Glu Val Phe Lys Gly Lys Lys Pro Asp Lys Asp Asn Arg Cys  
 145 150 155 160  
 Arg Tyr Ile Leu Lys Thr Lys Phe Arg Glu Met Trp Lys Ser Trp Pro  
 165 170 175  
 Gly Asp Ser Lys Glu Val Gln Val Met Ala Glu Arg Tyr Lys Met Leu  
 180 185 190  
 Ile Pro Phe Ser Asn Pro Arg Val Leu Pro Gly Pro Phe Ser Tyr Thr  
 195 200 205  
 Val Val Leu Tyr Gly Pro Ala Gly Leu Gly Lys Thr Thr Leu Ala Gln  
 210 215 220  
 Lys Leu Met Leu Asp Trp Ala Glu Asp Asn Leu Ile His Lys Phe Lys  
 225 230 235 240  
 Tyr Ala Phe Tyr Leu Ser Cys Arg Glu Leu Ser Arg Leu Gly Pro Cys  
 245 250 255  
 Ser Phe Ala Glu Leu Val Phe Arg Asp Trp Pro Glu Leu Gln Asp Asp  
 260 265 270  
 Ile Pro His Ile Leu Ala Gln Ala Arg Lys Ile Leu Phe Val Ile Asp  
 275 280 285  
 Gly Phe Asp Glu Leu Gly Ala Ala Pro Gly Ala Leu Ile Glu Asp Ile  
 290 295 300  
 Cys Gly Asp Trp Glu Lys Lys Lys Pro Val Pro Val Leu Leu Gly Ser  
 305 310 315 320  
 Leu Leu Asn Arg Val Met Leu Pro Lys Ala Ala Leu Leu Val Thr Thr  
 325 330 335  
 Arg Pro Arg Ala Leu Arg Asp Leu Arg Ile Leu Ala Glu Glu Pro Ile  
 340 345 350  
 Tyr Ile Arg Val Glu Gly Phe Leu Glu Glu Asp Arg Arg Ala Tyr Phe  
 355 360 365  
 Leu Arg His Phe Gly Asp Glu Asp Gln Ala Met Arg Ala Phe Glu Leu  
 370 375 380  
 Met Arg Ser Asn Ala Ala Leu Phe Gln Leu Gly Ser Ala Pro Ala Val  
 385 390 395 400  
 Cys Trp Ile Val Cys Thr Thr Leu Lys Leu Gln Met Glu Lys Gly Glu  
 405 410 415  
 Asp Pro Val Pro Thr Cys Leu Thr Arg Thr Gly Leu Phe Leu Arg Phe  
 420 425 430  
 Leu Cys Ser Arg Phe Pro Gln Gly Ala Gln Leu Arg Gly Ala Leu Arg  
 435 440 445  
 Thr Leu Ser Leu Leu Ala Ala Gln Gly Leu Trp Ala Gln Thr Ser Val  
 450 455 460  
 Leu His Arg Glu Asp Leu Glu Arg Leu Gly Val Gln Glu Ser Asp Leu  
 465 470 475 480  
 Arg Leu Phe Leu Asp Gly Asp Ile Leu Arg Gln Asp Arg Val Ser Lys  
 485 490 495  
 Gly Cys Tyr Ser Phe Ile His Leu Ser Phe Gln Gln Phe Leu Thr Ala  
 500 505 510  
 Leu Phe Tyr Thr Leu Glu Lys Glu Glu Glu Asp Arg Asp Gly His  
 515 520 525  
 Thr Trp Asp Ile Gly Asp Val Gln Lys Leu Leu Ser Gly Val Glu Arg  
 530 535 540  
 Leu Arg Asn Pro Asp Leu Ile Gln Ala Gly Tyr Tyr Ser Phe Gly Leu  
 545 550 555 560  
 Ala Asn Glu Lys Arg Ala Lys Glu Leu Glu Ala Thr Phe Gly Cys Arg

				565					570					575			
Met	Ser	Pro	Asp	Ile	Lys	Gln	Glu	Leu	Leu	Arg	Cys	Asp	Ile	Ser	Cys		
			580						585					590			
Lys	Gly	Gly	His	Ser	Thr	Val	Thr	Asp	Leu	Gln	Glu	Leu	Leu	Gly	Cys		
		595						600					605				
Leu	Tyr	Glu	Ser	Gln	Glu	Glu	Glu	Leu	Val	Lys	Glu	Val	Met	Ala	Gln		
	610					615					620						
Phe	Lys	Glu	Ile	Ser	Leu	His	Leu	Asn	Ala	Val	Asp	Val	Val	Pro	Ser		
625					630					635					640		
Ser	Phe	Cys	Val	Lys	His	Cys	Arg	Asn	Leu	Gln	Lys	Met	Ser	Leu	Gln		
				645					650					655			
Val	Ile	Lys	Glu	Asn	Leu	Pro	Glu	Asn	Val	Thr	Ala	Ser	Glu	Ser	Asp		
			660					665					670				
Ala	Glu	Val	Glu	Arg	Ser	Gln	Asp	Asp	Gln	His	Met	Leu	Pro	Phe	Trp		
		675					680					685					
Thr	Asp	Leu	Cys	Ser	Ile	Phe	Gly	Ser	Asn	Lys	Asp	Leu	Met	Gly	Leu		
	690					695					700						
Ala	Ile	Asn	Asp	Ser	Phe	Leu	Ser	Ala	Ser	Leu	Val	Arg	Ile	Leu	Cys		
705					710					715					720		
Glu	Gln	Ile	Ala	Ser	Asp	Thr	Cys	His	Leu	Gln	Arg	Val	Val	Phe	Lys		
				725					730					735			
Asn	Ile	Ser	Pro	Ala	Asp	Ala	His	Arg	Asn	Leu	Cys	Leu	Ala	Leu	Arg		
			740					745					750				
Gly	His	Lys	Thr	Val	Thr	Tyr	Leu	Thr	Leu	Gln	Gly	Asn	Asp	Gln	Asp		
	755						760					765					
Asp	Met	Phe	Pro	Ala	Leu	Cys	Glu	Val	Leu	Arg	His	Pro	Glu	Cys	Asn		
	770					775					780						
Leu	Arg	Tyr	Leu	Gly	Leu	Val	Ser	Cys	Ser	Ala	Thr	Thr	Gln	Gln	Trp		
785					790					795					800		
Ala	Asp	Leu	Ser	Leu	Ala	Leu	Glu	Val	Asn	Gln	Ser	Leu	Thr	Cys	Val		
				805					810					815			
Asn	Leu	Ser	Asp	Asn	Glu	Leu	Leu	Asp	Glu	Gly	Ala	Lys	Leu	Leu	Tyr		
			820					825					830				
Thr	Thr	Leu	Arg	His	Pro	Lys	Cys	Phe	Leu	Gln	Arg	Leu	Ser	Leu	Glu		
	835						840					845					
Asn	Cys	His	Leu	Thr	Glu	Ala	Asn	Cys	Lys	Asp	Leu	Ala	Ala	Val	Leu		
	850					855					860						
Val	Val	Ser	Arg	Glu	Leu	Thr	His	Leu	Cys	Leu	Ala	Lys	Asn	Pro	Ile		
865					870					875					880		
Gly	Asn	Thr	Gly	Val	Lys	Phe	Leu	Cys	Glu	Gly	Leu	Arg	Tyr	Pro	Glu		
				885					890					895			
Cys	Lys	Leu	Gln	Thr	Leu	Val	Leu	Trp	Asn	Cys	Asp	Ile	Thr	Ser	Asp		
			900					905					910				
Gly	Cys	Cys	Asp	Leu	Thr	Lys	Leu	Leu	Gln	Glu	Lys	Ser	Ser	Leu	Leu		
	915						920					925					
Cys	Leu	Asp	Leu	Gly	Leu	Asn	His	Ile	Gly	Val	Lys	Gly	Met	Lys	Phe		
	930					935					940						
Leu	Cys	Glu	Ala	Leu	Arg	Lys	Pro	Leu	Cys	Asn	Leu	Arg	Cys	Leu	Trp		
945					950					955					960		
Leu	Trp	Gly	Cys	Ser	Ile	Pro	Pro	Phe	Ser	Cys	Glu	Asp	Leu	Cys	Ser		
				965					970					975			
Ala	Leu	Ser	Cys	Asn	Gln	Ser	Leu	Val	Thr	Leu	Asp	Leu	Gly	Gln	Asn		
			980						985					990			
Pro	Leu	Gly	Ser	Ser	Gly	Val	Lys	Met	Leu	Phe	Glu	Thr	Leu	Thr	Cys		
	995						1000						1005				
Ser	Ser	Gly	Thr	Leu	Arg	Thr	Leu	Arg	Leu	Lys	Ile	Asp	Asp	Phe	Asn		
	1010					1015					1020						
Asp	Glu	Leu	Asn	Lys	Leu	Leu	Glu	Glu	Ile	Glu	Glu	Lys	Asn	Pro	Gln		
1025					1030					1035					1040		



Leu Ile Ile Asp Thr Glu Lys His His Pro Trp Ala Glu Arg Pro Ser  
 1045 1050 1055  
 Ser His Asp Phe Met Ile  
 1060

<210> 44  
 <211> 353  
 <212> PRT  
 <213> Homo sapiens

<400> 44  
 Met Thr Ile Phe His Pro Ile Thr Ser Ser Ile Gly Gln Pro Gly Cys  
 1 5 10 15  
 Gly Pro Lys Cys Lys Glu Thr Pro Leu Glu Leu Val Phe Val Ile Asp  
 20 25 30  
 Ser Ser Glu Ser Val Gly Pro Glu Asn Phe Gln Ile Ile Lys Asn Phe  
 35 40 45  
 Val Lys Thr Met Ala Asp Arg Val Ala Leu Asp Leu Ala Thr Ala Arg  
 50 55 60  
 Ile Gly Ile Ile Asn Tyr Ser His Lys Val Glu Lys Val Ala Asn Leu  
 65 70 75 80  
 Lys Gln Phe Ser Ser Lys Asp Asp Phe Lys Leu Ala Val Asp Asn Met  
 85 90 95  
 Gln Tyr Leu Gly Glu Gly Thr Tyr Thr Ala Thr Ala Leu Gln Ala Ala  
 100 105 110  
 Asn Asp Met Phe Glu Asp Ala Arg Pro Gly Val Lys Lys Val Ala Leu  
 115 120 125  
 Val Ile Thr Asp Gly Gln Thr Asp Ser Arg Asp Lys Glu Lys Leu Thr  
 130 135 140  
 Glu Val Val Lys Asn Ala Ser Asp Thr Asn Val Glu Ile Phe Val Ile  
 145 150 155 160  
 Gly Val Val Lys Lys Asn Asp Pro Asn Phe Glu Ile Phe His Lys Glu  
 165 170 175  
 Met Asn Leu Ile Ala Thr Asp Pro Glu His Val Tyr Gln Phe Asp Asp  
 180 185 190  
 Phe Phe Thr Leu Gln Asp Thr Leu Lys Gln Lys Leu Phe Gln Lys Ile  
 195 200 205  
 Cys Glu Asp Phe Asp Ser Tyr Leu Val Gln Ile Phe Gly Ser Ser Ser  
 210 215 220  
 Pro Gln Pro Gly Phe Gly Met Ser Gly Glu Glu Leu Ser Glu Ser Thr  
 225 230 235 240  
 Pro Glu Pro Gln Lys Glu Ile Ser Glu Ser Leu Ser Val Thr Arg Asp  
 245 250 255  
 Gln Asp Glu Asp Lys Ala Pro Glu Pro Thr Trp Ala Asp Asp Leu  
 260 265 270  
 Pro Ala Thr Thr Ser Ser Glu Ala Thr Thr Thr Pro Arg Pro Leu Leu  
 275 280 285  
 Ser Thr Pro Val Asp Gly Ala Glu Asp Pro Arg Cys Leu Glu Ala Leu  
 290 295 300  
 Lys Pro Gly Asn Cys Gly Glu Tyr Val Val Arg Trp Tyr Tyr Asp Lys  
 305 310 315 320  
 Gln Val Asn Ser Cys Ala Arg Phe Trp Phe Ser Gly Cys Asn Gly Ser  
 325 330 335  
 Gly Asn Arg Phe Asn Ser Glu Lys Glu Cys Gln Glu Thr Cys Ile Gln  
 340 345 350  
 Gly

<210> 45

<211> 448  
 <212> PRT  
 <213> Homo sapiens

<400> 45

Met	His	Glu	Val	Ile	Glu	Ser	Asp	Tyr	Glu	Gly	Arg	Asp	Lys	Thr	Leu	1	5	10	15
Ser	Cys	Leu	Val	Val	Gly	Val	Cys	Asp	Tyr	Ser	Thr	Arg	Met	Leu	Gly	20	25	30	
Arg	Asn	Asp	His	Thr	Ala	Val	Thr	Gly	Gln	Gln	Gly	Ala	Trp	Ser	Glu	35	40	45	
Ser	Ala	Ser	Leu	Asp	His	Ser	Pro	Ile	Leu	Ser	Phe	Leu	Pro	Gln	Glu	50	55	60	
Phe	Pro	Ala	Asp	Arg	Asp	Gly	Ser	Leu	Ala	Leu	His	Ser	Thr	Tyr	Glu	65	70	75	80
Ser	Leu	Arg	Leu	Ser	Ala	Ser	Ser	Trp	Thr	Val	Asn	Pro	Leu	Arg	Gly	85	90	95	
Ile	Asn	Met	Met	Pro	Ser	Ser	Leu	Ala	Pro	Ser	Ser	Gln	Gly	Cys	Gly	100	105	110	
Pro	Lys	Cys	Lys	Glu	Thr	Pro	Leu	Glu	Leu	Val	Phe	Val	Ile	Asp	Ser	115	120	125	
Ser	Glu	Ser	Val	Gly	Pro	Glu	Asn	Phe	Gln	Ile	Ile	Lys	Asn	Phe	Val	130	135	140	
Lys	Thr	Met	Ala	Asp	Arg	Val	Ala	Leu	Asp	Leu	Ala	Thr	Ala	Arg	Ile	145	150	155	160
Gly	Ile	Ile	Asn	Tyr	Ser	His	Lys	Val	Glu	Lys	Val	Ala	Asn	Leu	Lys	165	170	175	
Gln	Phe	Ser	Ser	Lys	Asp	Asp	Phe	Lys	Leu	Ala	Val	Asp	Asn	Met	Gln	180	185	190	
Tyr	Leu	Gly	Glu	Gly	Thr	Tyr	Thr	Ala	Thr	Ala	Leu	Gln	Ala	Ala	Asn	195	200	205	
Asp	Met	Phe	Glu	Asp	Ala	Arg	Pro	Gly	Val	Lys	Lys	Val	Ala	Leu	Val	210	215	220	
Ile	Thr	Asp	Gly	Gln	Thr	Asp	Ser	Arg	Asp	Lys	Glu	Lys	Leu	Thr	Glu	225	230	235	240
Val	Val	Lys	Asn	Ala	Ser	Asp	Thr	Asn	Val	Glu	Ile	Phe	Val	Ile	Gly	245	250	255	
Val	Val	Lys	Lys	Asn	Asp	Pro	Asn	Phe	Glu	Ile	Phe	His	Lys	Glu	Met	260	265	270	
Asn	Leu	Ile	Ala	Thr	Asp	Pro	Glu	His	Val	Tyr	Gln	Phe	Asp	Asp	Phe	275	280	285	
Phe	Thr	Leu	Gln	Asp	Thr	Leu	Lys	Gln	Lys	Leu	Phe	Gln	Lys	Ile	Cys	290	295	300	
Glu	Asp	Phe	Asp	Ser	Tyr	Leu	Val	Gln	Ile	Phe	Gly	Ser	Ser	Ser	Pro	305	310	315	320
Gln	Pro	Gly	Phe	Gly	Met	Ser	Gly	Glu	Glu	Leu	Ser	Glu	Ser	Thr	Pro	325	330	335	
Glu	Pro	Gln	Lys	Glu	Ile	Ser	Glu	Ser	Leu	Ser	Val	Thr	Arg	Asp	Gln	340	345	350	
Asp	Glu	Asp	Asp	Lys	Ala	Pro	Glu	Pro	Thr	Trp	Ala	Asp	Asp	Leu	Pro	355	360	365	
Ala	Thr	Thr	Ser	Ser	Glu	Ala	Thr	Thr	Thr	Pro	Arg	Pro	Leu	Leu	Ser	370	375	380	
Thr	Pro	Val	Asp	Gly	Ala	Glu	Asp	Pro	Arg	Cys	Leu	Glu	Ala	Leu	Lys	385	390	395	400
Pro	Gly	Asn	Cys	Gly	Glu	Tyr	Val	Val	Arg	Trp	Tyr	Tyr	Asp	Lys	Gln	405	410	415	
Val	Asn	Ser	Cys	Ala	Arg	Phe	Trp	Phe	Ser	Gly	Cys	Asn	Gly	Ser	Gly	420	425	430	

35/60

Asn Arg Phe Asn Ser Glu Lys Glu Cys Gln Glu Thr Cys Ile Gln Gly  
 435 440 445

<210> 46  
 <211> 493  
 <212> PRT  
 <213> Homo sapiens

<400> 46

Met Leu Pro Ala Ala Pro Ser Gly Cys Pro Gln Leu Cys Arg Cys Glu  
 1 5 10 15  
 Gly Arg Leu Leu Tyr Cys Glu Ala Leu Asn Leu Thr Glu Ala Pro His  
 20 25 30  
 Asn Leu Ser Gly Leu Leu Gly Leu Ser Leu Arg Tyr Asn Ser Leu Ser  
 35 40 45  
 Glu Leu Arg Ala Gly Gln Phe Thr Gly Leu Met Gln Leu Thr Trp Leu  
 50 55 60  
 Tyr Leu Asp His Asn His Ile Cys Ser Val Gln Gly Asp Ala Phe Gln  
 65 70 75 80  
 Lys Leu Arg Arg Val Lys Glu Leu Thr Leu Ser Ser Asn Gln Ile Thr  
 85 90 95  
 Gln Leu Pro Asn Thr Thr Phe Arg Pro Met Pro Asn Leu Arg Ser Val  
 100 105 110  
 Asp Leu Ser Tyr Asn Lys Leu Gln Ala Leu Ala Pro Asp Leu Phe His  
 115 120 125  
 Gly Leu Arg Lys Leu Thr Thr Leu His Met Arg Ala Asn Ala Ile Gln  
 130 135 140  
 Phe Val Pro Val Arg Ile Phe Gln Asp Cys Arg Ser Leu Lys Phe Leu  
 145 150 155 160  
 Asp Ile Gly Tyr Asn Gln Leu Lys Ser Leu Ala Arg Asn Ser Phe Ala  
 165 170 175  
 Gly Leu Phe Lys Leu Thr Glu Leu His Leu Glu His Asn Asp Leu Val  
 180 185 190  
 Lys Val Asn Phe Ala His Phe Pro Arg Leu Ile Ser Leu His Ser Leu  
 195 200 205  
 Cys Leu Arg Arg Asn Lys Val Ala Ile Val Val Ser Ser Leu Asp Trp  
 210 215 220  
 Val Trp Asn Leu Glu Lys Met Asp Leu Ser Gly Asn Glu Ile Glu Tyr  
 225 230 235 240  
 Met Glu Pro His Val Phe Glu Thr Val Pro His Leu Gln Ser Leu Gln  
 245 250 255  
 Leu Asp Ser Asn Arg Leu Thr Tyr Ile Glu Pro Arg Ile Leu Asn Ser  
 260 265 270  
 Trp Lys Ser Leu Thr Ser Ile Thr Leu Ala Gly Asn Leu Trp Asp Cys  
 275 280 285  
 Gly Arg Asn Val Cys Ala Leu Ala Ser Trp Leu Asn Asn Phe Gln Gly  
 290 295 300  
 Arg Tyr Asp Gly Asn Leu Gln Cys Ala Ser Pro Glu Tyr Ala Gln Gly  
 305 310 315 320  
 Glu Asp Val Leu Asp Ala Val Tyr Ala Phe His Leu Cys Glu Asp Gly  
 325 330 335  
 Ala Glu Pro Thr Ser Gly His Leu Leu Ser Ala Val Thr Asn Arg Ser  
 340 345 350  
 Asp Leu Gly Pro Pro Ala Arg Arg Ala Thr Thr Ala Ser Arg Thr Gly  
 355 360 365  
 Gly Glu Gly Gln His Asp Gly Thr Phe Lys Pro Ala Thr Gly Gly Phe  
 370 375 380  
 Pro Ala Gly Glu His Ala Lys Asn Pro Val Gln Ile His Lys Val Val  
 385 390 395 400

Thr Gly Thr Met Ala Phe Ile Phe Ser Phe Leu Met Val Val Leu Val  
 405 410 415  
 Leu Tyr Val Ser Trp Lys Cys Phe Pro Ala Ser Leu Arg Gln Leu Arg  
 420 425 430  
 Gln Cys Phe Val Thr Gln Arg Arg Lys Gln Lys Gln Lys Gln Thr Met  
 435 440 445  
 His Gln Met Ala Ala Met Ser Ala Gln Glu Tyr Tyr Val Asp Tyr Lys  
 450 455 460  
 Pro Asn His Ile Glu Gly Ala Leu Val Ile Ile Asn Glu Tyr Gly Ser  
 465 470 475 480  
 Cys Thr Cys His Gln Gln Pro Ala Arg Glu Cys Glu Val  
 485 490

<210> 47  
 <211> 548  
 <212> PRT  
 <213> Homo sapiens

<400> 47  
 Met Pro Ala Leu Arg Pro Leu Leu Pro Leu Leu Leu Leu Leu Arg Leu  
 1 5 10 15  
 Thr Ser Gly Ala Gly Leu Leu Pro Gly Leu Gly Ser His Pro Gly Val  
 20 25 30  
 Cys Pro Asn Gln Leu Ser Pro Asn Leu Trp Val Asp Ala Gln Ser Thr  
 35 40 45  
 Cys Glu Arg Glu Cys Ser Arg Asp Gln Asp Cys Ala Ala Ala Glu Lys  
 50 55 60  
 Cys Cys Ile Asn Val Cys Gly Leu His Ser Cys Val Ala Ala Arg Phe  
 65 70 75 80  
 Pro Gly Ser Pro Ala Ala Pro Thr Thr Ala Ala Ser Cys Glu Gly Phe  
 85 90 95  
 Val Cys Pro Gln Gln Gly Ser Asp Cys Asp Ile Trp Asp Gly Gln Pro  
 100 105 110  
 Val Cys Arg Cys Arg Asp Arg Cys Glu Lys Glu Pro Ser Phe Thr Cys  
 115 120 125  
 Ala Ser Asp Gly Leu Thr Tyr Tyr Asn Arg Cys Tyr Met Asp Ala Glu  
 130 135 140  
 Ala Cys Leu Arg Gly Leu His Leu His Ile Val Pro Cys Lys His Val  
 145 150 155 160  
 Leu Ser Trp Pro Pro Ser Ser Pro Gly Pro Pro Glu Thr Thr Ala Arg  
 165 170 175  
 Pro Thr Pro Gly Ala Ala Pro Val Pro Pro Ala Leu Tyr Ser Ser Pro  
 180 185 190  
 Ser Pro Gln Ala Val Gln Val Gly Gly Thr Ala Ser Leu His Cys Asp  
 195 200 205  
 Val Ser Gly Arg Pro Pro Pro Ala Val Thr Trp Glu Lys Gln Ser His  
 210 215 220  
 Gln Arg Glu Asn Leu Ile Met Arg Pro Asp Gln Met Tyr Gly Asn Val  
 225 230 235 240  
 Val Val Thr Ser Ile Gly Gln Leu Val Leu Tyr Asn Ala Arg Pro Glu  
 245 250 255  
 Asp Ala Gly Leu Tyr Thr Cys Thr Ala Arg Asn Ala Ala Gly Leu Leu  
 260 265 270  
 Arg Ala Asp Phe Pro Leu Ser Val Val Gln Arg Glu Pro Ala Arg Asp  
 275 280 285  
 Ala Ala Pro Ser Ile Pro Ala Pro Ala Glu Cys Leu Pro Asp Val Gln  
 290 295 300  
 Ala Cys Thr Gly Pro Thr Ser Pro His Leu Val Leu Trp His Tyr Asp  
 305 310 315 320

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<210> 48
<211> 286
<212> PRT
<213> Homo sapiens
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	<400>			48												
Met	Ala	Phe	Val	Ala	Ile	Val	Val	Ser	Asn	Phe	Gly	Leu	Ser	Gly	Gln	
1				5				10						15		
Pro	His	Gly	Gly	Phe	Asn	Ser	Gln	Asp	Gln	Asn	Asp	Gln	Gly	Pro	Ser	
			20					25					30			
Val	Pro	Val	Ser	Leu	Leu	Asp	Arg	Thr	Thr	Gly	Gly	Gly	Ser	Ala	Leu	
			35				40					45				
Cys	Phe	Leu	Ala	Gly	Ile	Asp	Tyr	Lys	Thr	Thr	Thr	Ile	Leu	Leu	Asp	
	50					55					60					
Gly	Arg	Arg	Val	Lys	Leu	Glu	Leu	Trp	Asp	Thr	Ser	Gly	Gln	Gly	Arg	
65				70						75				80		
Phe	Cys	Thr	Ile	Phe	Arg	Ser	Tyr	Ser	Arg	Gly	Ala	Gln	Gly	Ile	Leu	
				85					90					95		
Leu	Val	Tyr	Asp	Ile	Thr	Asn	Arg	Trp	Ser	Phe	Asp	Gly	Ile	Asp	Arg	
			100					105					110			
Trp	Ile	Lys	Glu	Ile	Asp	Glu	His	Ala	Pro	Gly	Val	Pro	Arg	Ile	Leu	
		115				120						125				
Val	Gly	Asn	Arg	Leu	His	Leu	Ala	Phe	Lys	Arg	Gln	Val	Pro	Thr	Glu	
	130					135					140					
Gln	Ala	Arg	Ala	Tyr	Ala	Glu	Lys	Asn	Cys	Met	Thr	Phe	Phe	Glu	Val	
145				150					155					160		
Ser	Pro	Leu	Cys	Asn	Phe	Asn	Val	Ile	Glu	Ser	Phe	Thr	Glu	Leu	Ser	
				165					170					175		

Arg	Ile	Val	Leu	Met	Arg	His	Gly	Met	Glu	Lys	Ile	Trp	Arg	Pro	Asn
			180					185					190		
Arg	Val	Phe	Ser	Leu	Gln	Asp	Leu	Cys	Cys	Arg	Ala	Ile	Val	Ser	Cys
		195					200					205			
Thr	Pro	Val	His	Leu	Ile	Asp	Lys	Leu	Pro	Leu	Pro	Val	Thr	Ile	Lys
	210					215					220				
Ser	His	Leu	Lys	Ser	Phe	Ser	Met	Ala	Asn	Gly	Met	Asn	Ala	Val	Met
225					230					235				240	
Met	His	Gly	Arg	Ser	Tyr	Ser	Leu	Ala	Ser	Gly	Ala	Gly	Gly	Gly	Gly
				245					250					255	
Ser	Lys	Gly	Asn	Ser	Leu	Lys	Arg	Ser	Lys	Ser	Ile	Arg	Pro	Pro	Gln
			260					265					270		
Ser	Pro	Pro	Gln	Asn	Cys	Ser	Arg	Ser	Asn	Cys	Lys	Ile	Ser		
		275					280					285			

<210> 49  
 <211> 172  
 <212> PRT  
 <213> Homo sapiens

<400> 49

Met	Gly	Ile	Pro	Ile	Pro	Ile	Ile	Pro	His	His	Pro	Gln	Ala	Arg	Val
1				5				10					15		
Ala	Ser	Pro	Gln	Ala	Leu	Met	Asp	Lys	Trp	Pro	Trp	Lys	Ala	Ser	Ser
			20					25					30		
Ala	Ala	Pro	Gly	Phe	Cys	His	His	Pro	Ser	Thr	Lys	Trp	Ser	Arg	Asp
		35					40					45			
Pro	Gly	Arg	His	Pro	Glu	Ser	Pro	His	Arg	Gly	Gly	Ser	Gly	Val	His
	50					55					60				
Arg	Arg	Ser	Arg	Glu	Pro	Ala	Pro	His	Pro	Ala	Ser	Glu	Glu	Ser	Ser
65				70						75				80	
Phe	Pro	Trp	Leu	Glu	Asp	Pro	Val	Met	Lys	Tyr	Val	Gly	Lys	Gly	Gly
			85						90				95		
Tyr	Asn	Cys	Thr	Leu	Ser	Lys	Thr	Glu	Phe	Leu	Ser	Phe	Met	Asn	Ala
			100					105					110		
Glu	Leu	Ala	Phe	Thr	Lys	Asn	Gln	Lys	Asp	Pro	Gly	Val	Leu	His	
		115				120					125				
Arg	Met	Met	Lys	Lys	Leu	Gly	Thr	Asn	Asn	Asp	Gly	Gln	Leu	Asp	Phe
	130					135					140				
Ser	Glu	Phe	Leu	Asn	Leu	Ile	Gly	Gly	Leu	Ala	Met	Ala	Cys	His	Asp
145				150						155				160	
Ser	Phe	Leu	Lys	Ala	Val	Pro	Ser	Gln	Lys	Arg	Thr				
			165						170						

<210> 50  
 <211> 103  
 <212> PRT  
 <213> Homo sapiens

<400> 50

Leu	Gln	Lys	Ser	Pro	Ala	Leu	Gln	Arg	Leu	Ser	Ile	Glu	Ser	Leu	Ile
1				5					10					15	
Ser	Leu	Phe	Gln	Lys	Tyr	Val	Gly	Lys	Gly	Gly	Tyr	Asn	Cys	Thr	Leu
			20					25					30		
Ser	Lys	Thr	Glu	Phe	Leu	Ser	Phe	Met	Asn	Ala	Glu	Leu	Ala	Ala	Phe
		35					40					45			
Thr	Lys	Asn	Gln	Lys	Asp	Pro	Gly	Val	Leu	His	Arg	Met	Met	Lys	Lys
	50					55					60				
Leu	Gly	Thr	Asn	Asn	Asp	Gly	Gln	Leu	Asp	Phe	Ser	Glu	Phe	Leu	Asn



370		375		380
Lys Cys Pro His Lys Asn Ile Thr Ala Glu Asp Cys Ser His Ser Gln				
385		390		395
Asp Ala Gly Val Arg Cys Asn Leu Pro Tyr Thr Gly Ala Glu Thr Arg				
		405		410
Ile Arg Leu Ser Gly Gly Arg Ser Gln His Glu Gly Arg Val Glu Val				
		420		425
Gln Ile Gly Gly Pro Gly Pro Leu Arg Trp Gly Leu Ile Cys Gly Asp				
		435		440
Asp Trp Gly Thr Leu Glu Ala Met Val Ala Cys Arg Gln Leu Gly Leu				
		450		455
Gly Tyr Ala Asn His Gly Leu Gln Glu Thr Trp Tyr Trp Asp Ser Gly				
465		470		475
Asn Ile Thr Glu Val Val Met Ser Gly Val Arg Cys Thr Gly Thr Glu				
		485		490
Leu Ser Leu Asp Gln Cys Ala His His Gly Thr His Ile Thr Cys Lys				
		500		505
Arg Thr Gly Thr Arg Phe Thr Ala Gly Val Ile Cys Ser Glu Thr Ala				
		515		520
Ser Asp Leu Leu Leu His Ser Ala Leu Val Gln Glu Thr Ala Tyr Ile				
		530		535
Glu Asp Arg Pro Leu His Met Leu Tyr Cys Ala Ala Glu Glu Asn Cys				
545		550		555
Leu Ala Ser Ser Ala Arg Ser Ala Asn Trp Pro Tyr Gly His Arg Arg				
		565		570
Leu Leu Arg Phe Ser Ser Gln Ile His Asn Leu Gly Arg Ala Asp Phe				
		580		585
Arg Pro Lys Ala Gly Arg His Ser Trp Val Trp His Glu Cys His Gly				
		595		600
His Tyr His Ser Met Asp Ile Phe Thr His Tyr Asp Ile Leu Thr Pro				
		610		615
Asn Gly Thr Lys Val Ala Glu Gly His Lys Ala Ser Phe Cys Leu Glu				
625		630		635
Asp Thr Glu Cys Gln Glu Asp Val Ser Lys Arg Tyr Glu Cys Ala Asn				
		645		650
Phe Gly Glu Gln Gly Ile Thr Val Gly Cys Trp Asp Leu Tyr Arg His				
		660		665
Asp Ile Asp Cys Gln Trp Ile Asp Ile Thr Asp Val Lys Pro Gly Asn				
		675		680
Tyr Ile Leu Gln Val Val Ile Asn Pro Asn Phe Glu Val Ala Glu Ser				
		690		695
Asp Phe Thr Asn Asn Ala Met Lys Cys Asn Cys Lys Tyr Asp Gly His				
705		710		715
Arg Ile Trp Val His Asn Cys His Ile Gly Asp Ala Phe Ser Glu Glu				
		725		730
Ala Asn Arg Arg Phe Glu Arg Tyr Pro Gly Gln Thr Ser Asn Gln Ile				
		740		745
Ile				750

<210> 52  
 <211> 114  
 <212> PRT  
 <213> Homo sapiens

<400> 52  
 Met Glu Ser Ala Ala Gln Leu Gly Pro Gln Val Pro Val Ala Leu Ser  
 1 5 10 15  
 Trp Met Arg Asp Gln Gly Gln Gly His Cys Ile Thr Thr Leu Cys Cys



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                20                25                30
Phe Pro Glu Arg Tyr Ala Gly Arg Asp His Asn Ser Cys Lys Leu Ser
      35                40                45
Gln Arg Gly Phe Leu Asn Phe Met Asn Thr Val Leu Val Ala Phe Thr
      50                55                60
Lys Asn Gln Lys Gly Ser Gly Ala Leu Asp Cys Met Met Lys Lys Leu
      65                70                75                80
Asp Phe Asn Cys Asp Gly Gln Asp Phe Gln Asp Phe Leu Ser Leu Thr
      85                90                95
Asp Gly Val Ala Val Ala Cys Pro Asp Ser Phe Ile Pro Ala Gly His
      100                105                110
Ala Pro

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<210> 53
<211> 106
<212> PRT
<213> Homo sapiens

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<400> 53
Met Ala Lys Ile Ser Gly Cys Thr Glu Ile Ala Trp Trp Cys Ile Thr
  1                5                10                15
Thr Leu Cys Cys Phe Pro Glu Arg Tyr Ala Gly Arg Asp His Asn Ser
      20                25                30
Cys Lys Leu Ser Gln Arg Gly Phe Leu Asn Phe Met Asn Thr Val Leu
      35                40                45
Val Ala Phe Thr Lys Asn Gln Lys Gly Ser Gly Ala Leu Asp Cys Met
      50                55                60
Met Lys Lys Leu Asp Phe Asn Cys Asp Gly Gln Leu Asp Phe Gln Asp
      65                70                75                80
Phe Leu Ser Leu Thr Asp Gly Val Ala Val Ala Cys Pro Asp Ser Phe
      85                90                95
Ile Pro Ala Gly His Ala His Glu Arg Ile
      100                105

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<210> 54
<211> 643
<212> PRT
<213> Homo sapiens

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<400> 54
Met Ala Leu Ala Gly Pro Cys Pro Ser Ser Thr Ala Ser Leu Leu Pro
  1                5                10                15
Ser Thr Gln Ala Leu Pro Thr Ile Asn Ser Phe Leu Lys Ile Ala Ser
      20                25                30
Lys Pro Lys Ser Thr Leu Asp Arg Ala Val Gly Lys Ala Ser Ser Ile
      35                40                45
Leu Ala Leu Lys Ser Arg Ala Ser Ala Lys Arg Ser Val Leu Leu Pro
      50                55                60
Ile Leu Ala Leu Trp Ala Gly Ser Cys Ser Gly Gly Ala Pro Pro Thr
      65                70                75                80
Pro Met Gly Leu Ala Thr Leu Gln Leu Leu Pro Ser Pro Pro Gly Ala
      85                90                95
Pro Asp Gly Gln Leu Gln Pro Ile Pro Gly Ile Gly His Pro Asp Lys
      100                105                110
Pro Glu Ala Gly Lys Leu Asp Gln Leu Arg Asp Gln Pro Thr Pro Lys
      115                120                125
Gln Gly Ala Gln Gly Thr Pro Thr Gln Ser Pro Ser Thr Gly Trp Lys
      130                135                140

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Ala Leu Pro Arg Pro Gly Leu Ala Leu Arg Lys Glu Ser Pro Pro Val  
 145 150 155 160  
 Thr Leu Glu Gln Glu Gln Gly His Asn Lys Gly Leu Val Ala Glu Trp  
 165 170 175  
 Ala Gln Pro Gln Ala Thr Ala Ala Met Arg Ala Gly Ala Gly Lys Pro  
 180 185 190  
 Glu Ala Leu Lys Leu Arg Pro Trp Gln Ala Gly Arg Asp Pro Gln Ala  
 195 200 205  
 Gln Glu Gly Ala Ala Val Thr Glu Glu Asp Gln Gly Gln Arg Thr Gly  
 210 215 220  
 Gly Arg Glu Asp Lys Gly Arg Gly Leu Lys Pro Arg Arg Pro Pro Lys  
 225 230 235 240  
 Gly Thr Ser His Gln Pro Gly Leu Arg Ile Arg Arg Pro Gln Lys Asp  
 245 250 255  
 Arg Ser Arg Gly Gln Gly Gly Gly Gly Ser Thr Ser Lys Thr Pro Gly  
 260 265 270  
 His Gly Trp Lys Arg Pro Gly Ser Thr His Gly His Arg His Arg His  
 275 280 285  
 Ala Asp Leu Gly Thr Thr Gln Gln Ala Met Pro Ser Leu Pro Ala Ser  
 290 295 300  
 Cys Leu Leu Ala Gln Ala Val Ile Ala Cys Gly Asn Val Lys Met Lys  
 305 310 315 320  
 His Val Pro Ala Leu Thr His Pro Gly Leu Thr Thr Leu Tyr Leu Ala  
 325 330 335  
 Glu Asn Glu Ile Ala Lys Ile Pro Ala His Thr Phe Leu Gly Leu Pro  
 340 345 350  
 Asn Leu Glu Trp Leu Asp Leu Ser Lys Asn Lys Leu Asp Pro Arg Gly  
 355 360 365  
 Leu His Pro His Ala Phe Lys Asn Leu Met Arg Leu Lys Arg Leu Asn  
 370 375 380  
 Leu Val Gly Asn Ser Leu Thr Thr Val Pro Ala Leu Pro Ala Ser Leu  
 385 390 395 400  
 Gln Glu Leu Lys Leu Asn Asp Asn Leu Leu Gln Gly Leu Gln Gly Ser  
 405 410 415  
 Ser Phe Arg Gly Leu Ser Gln Leu Leu Thr Leu Glu Glu Leu His Leu  
 420 425 430  
 Gly Thr Asn Leu Ile Glu Glu Val Ala Glu Gly Ala Leu Ser His Ile  
 435 440 445  
 His Ser Leu Ser Val Leu Val Leu Ser His Asn Trp Leu Gln Glu His  
 450 455 460  
 Trp Leu Ala Pro Arg Ala Trp Ile His Leu Pro Lys Leu Glu Thr Leu  
 465 470 475 480  
 Asp Leu Ser Tyr Asn Arg Leu Val His Val Pro Arg Phe Leu Pro Arg  
 485 490 495  
 Gly Leu Arg Arg Leu Thr Leu His His Asp His Ile Glu Arg Ile Pro  
 500 505 510  
 Gly Tyr Ala Phe Ala His Met Lys Pro Gly Leu Glu Phe Leu His Leu  
 515 520 525  
 Ser His Asn Arg Leu Gln Ala Asp Gly Ile His Ser Val Ser Phe Leu  
 530 535 540  
 Gly Leu Arg Ala Ser Leu Ala Glu Leu Leu Leu Asp His Asn Gln Val  
 545 550 555 560  
 Gln Ala Ile Pro Arg Gly Leu Leu Gly Leu Lys Gly Leu Gln Val Leu  
 565 570 575  
 Gly Leu Ser His Asn Arg Ile Arg Gln Val Pro Leu Asn Ser Ile Cys  
 580 585 590  
 Asp Met Arg Val Ala Gln Asp Ser Asn Leu Thr Ser Thr His Leu Glu  
 595 600 605  
 Asn Asn Leu Ile Asp Arg Arg Arg Ile Pro Pro Thr Ala Phe Ser Cys

610	615	620
Thr Arg Ala Tyr His Ser Val Val Leu Gln Pro Gln Arg Arg Gly Glu		
625	630	635
Glu Gly Ser		640

<210> 55  
 <211> 653  
 <212> PRT  
 <213> Homo sapiens

<400> 55

Met	Ala	Gly	Cys	Pro	Gly	Thr	Gly	Gln	Ser	Gly	Gln	Gln	Glu	Tyr	His
1			5						10					15	
Ser	Pro	Gly	Ala	His	Pro	Ala	Lys	Arg	Ser	Val	Leu	Leu	Pro	Ile	Leu
			20					25					30		
Ala	Leu	Trp	Ala	Gly	Ser	Cys	Ser	Gly	Gly	Ala	Pro	Pro	Thr	Pro	Met
		35					40					45			
Gly	Leu	Ala	Thr	Leu	Gln	Leu	Leu	Pro	Ser	Pro	Pro	Gly	Ala	Pro	Asp
	50					55					60				
Gly	Gln	Leu	Gln	Pro	Ile	Pro	Gly	Ile	Gly	His	Pro	Asp	Lys	Pro	Glu
65					70					75					80
Ala	Gly	Lys	Leu	Asp	Gln	Leu	Arg	Asp	Gln	Pro	Thr	Pro	Lys	Gln	Gly
				85					90					95	
Ala	Gln	Gly	Thr	Pro	Thr	Gln	Ser	Pro	Ser	Thr	Gly	Trp	Lys	Ala	Leu
			100					105					110		
Pro	Arg	Pro	Gly	Leu	Ala	Leu	Arg	Lys	Glu	Ser	Pro	Pro	Val	Thr	Leu
		115					120					125			
Glu	Gln	Glu	Gln	Gly	His	Asn	Lys	Gly	Leu	Val	Ala	Glu	Trp	Ala	Gln
	130					135					140				
Pro	Gln	Ala	Thr	Ala	Ala	Met	Arg	Ala	Gly	Ala	Gly	Lys	Pro	Glu	Ala
145					150					155					160
Leu	Lys	Leu	Arg	Pro	Trp	Gln	Ala	Gly	Arg	Asp	Pro	Gln	Ala	Gln	Glu
				165					170					175	
Gly	Ala	Ala	Val	Thr	Glu	Glu	Asp	Gln	Gly	Gln	Arg	Thr	Gly	Gly	Arg
			180				185						190		
Glu	Asp	Lys	Gly	Arg	Gly	Leu	Lys	Pro	Arg	Arg	Pro	Pro	Lys	Gly	Thr
		195					200					205			
Ser	His	Gln	Pro	Gly	Leu	Arg	Ile	Arg	Arg	Pro	Gln	Lys	Asp	Arg	Ser
	210					215					220				
Arg	Gly	Gln	Gly	Gly	Gly	Gly	Ser	Thr	Ser	Lys	Thr	Pro	Gly	His	Gly
225					230					235					240
Trp	Lys	Arg	Pro	Gly	Ser	Thr	His	Gly	His	Arg	His	Arg	His	Ala	Asp
				245					250					255	
Leu	Gly	Thr	Thr	Gln	Gln	Ala	Met	Pro	Ser	Leu	Pro	Ala	Ser	Cys	Leu
			260				265						270		
Leu	Ala	Gln	Ala	Val	Ile	Ala	Cys	Gly	Asn	Val	Lys	Met	Lys	His	Val
		275					280					285			
Pro	Ala	Leu	Thr	His	Pro	Gly	Leu	Thr	Thr	Leu	Tyr	Leu	Ala	Glu	Asn
	290					295					300				
Glu	Ile	Ala	Lys	Ile	Pro	Ala	His	Thr	Phe	Leu	Gly	Leu	Pro	Asn	Leu
305					310					315					320
Glu	Trp	Leu	Asp	Leu	Ser	Lys	Asn	Lys	Leu	Asp	Pro	Arg	Gly	Leu	His
				325					330					335	
Pro	His	Ala	Phe	Lys	Asn	Leu	Met	Arg	Leu	Lys	Arg	Leu	Asn	Leu	Val
			340				345					350			
Gly	Asn	Ser	Leu	Thr	Thr	Val	Pro	Ala	Leu	Pro	Ala	Ser	Leu	Gln	Glu
		355				360						365			
Leu	Lys	Leu	Asn	Asp	Asn	Leu	Leu	Gln	Gly	Leu	Gln	Gly	Ser	Ser	Phe

370	375	380
Arg Gly Leu Ser Gln Leu	Leu Thr Leu Glu Val	Glu Gly Asn Gln Leu
385	390	400
Arg Asp Arg Asp Ile Ser	Pro Leu Ala Phe Gln	Pro Leu Cys Ser Leu
405	410	415
Leu Tyr Leu Arg Leu Asp	Arg Asn Arg Leu Arg	Ala Ile Pro Arg Gly
420	425	430
Leu Pro Ser Ser Leu Gln	Glu Leu His Leu Gly	Thr Asn Leu Ile Glu
435	440	445
Glu Val Ala Glu Gly Ala	Leu Ser His Ile His	Ser Leu Ser Val Leu
450	455	460
Val Leu Ser His Asn Trp	Leu Gln Glu His Trp	Leu Ala Pro Arg Ala
465	470	475
Trp Ile His Leu Pro Lys	Leu Glu Thr Leu Asp	Leu Ser Tyr Asn Arg
485	490	495
Leu Val His Val Pro Arg	Phe Leu Pro Arg Gly	Leu Arg Arg Leu Thr
500	505	510
Leu His His Asp His Ile	Glu Arg Ile Pro Gly	Tyr Ala Phe Ala His
515	520	525
Met Lys Pro Gly Leu Glu	Phe Leu His Leu Ser	His Asn Arg Leu Gln
530	535	540
Ala Asp Gly Ile His Ser	Val Ser Phe Leu Gly	Leu Arg Ala Ser Leu
545	550	555
Ala Glu Leu Leu Leu Asp	His Asn Gln Val Gln	Ala Ile Pro Arg Gly
565	570	575
Leu Leu Gly Leu Lys Gly	Leu Gln Val Leu Gly	Leu Ser His Asn Arg
580	585	590
Ile Arg Gln Val Pro Leu	Asn Ser Ile Cys Asp	Met Arg Val Ala Gln
595	600	605
Asp Ser Asn Leu Thr Ser	Thr His Leu Glu Asn	Asn Leu Ile Asp Arg
610	615	620
Arg Arg Ile Pro Pro Thr	Ala Phe Ser Cys Thr	Arg Ala Tyr His Ser
625	630	635
Val Val Leu Gln Pro Gln	Arg Arg Gly Glu Gly	Ser
645	650	

<210> 56  
 <211> 305  
 <212> PRT  
 <213> Homo sapiens

<400> 56

Met Gly Ala Arg Gly Ala	Leu Leu Leu Ala Leu	Leu Leu Ala Arg Ala
1	5	10
Gly Leu Gly Lys Pro Glu	Ser Gln Glu Glu Leu	Leu Ser Glu Ala
20	25	30
Cys Gly His Arg Glu Ile	His Ala Leu Val Ala	Gly Gly Val Glu Ser
35	40	45
Ala Arg Gly Arg Trp Pro	Trp Gln Ala Ser Leu	Arg Leu Arg Arg Arg
50	55	60
His Arg Cys Gly Gly Ser	Leu Leu Ser Arg Arg	Trp Val Leu Ser Ala
65	70	75
Ala His Cys Phe Gln Lys	His Tyr Tyr Pro Ser	Glu Trp Thr Val Gln
85	90	95
Leu Gly Glu Leu Thr Ser	Arg Pro Thr Pro Trp	Asn Leu Arg Ala Tyr
100	105	110
Ser Ser Arg Tyr Lys Val	Gln Asp Ile Ile Val	Asn Pro Asp Ala Leu
115	120	125
Gly Val Leu Arg Asn Asp	Ile Ala Leu Leu Arg	Leu Ala Ser Ser Val

130	135	140
Thr Tyr Asn Ala Tyr Ile Gln Pro Ile Cys Ile Glu Ser Ser Thr Phe		
145	150	155
Asn Phe Val His Arg Pro Asp Cys Trp Val Thr Gly Trp Gly Leu Ile		160
	165	170
Ser Pro Ser Gly Thr Pro Leu Pro Pro Tyr Asn Leu Arg Glu Ala		175
	180	185
Gln Val Thr Ile Leu Asn Asn Thr Arg Cys Asn Tyr Leu Phe Glu Gln		190
	195	200
Pro Ser Ser Arg Ser Met Ile Trp Asp Ser Met Phe Cys Ala Gly Ala		205
	210	215
Glu Asp Gly Ser Val Asp Thr Cys Lys Gly Asp Ser Gly Gly Pro Leu		220
225	230	235
Val Cys Asp Lys Asp Gly Leu Trp Tyr Gln Val Gly Ile Val Ser Trp		240
	245	250
Gly Met Asp Cys Gly Gln Pro Asn Arg Pro Gly Val Tyr Thr Asn Ile		255
	260	265
Ser Val Tyr Phe His Trp Ile Arg Arg Val Met Ser His Ser Thr Pro		270
	275	280
Arg Pro Asn Pro Ser Gln Leu Leu Leu Leu Leu Ala Leu Leu Trp Ala		285
	290	295
Pro		300
305		

<210> 57  
 <211> 387  
 <212> PRT  
 <213> Homo sapiens

<400> 57
Met Arg Val Thr Trp Asn His Gly Pro Pro Cys Pro Ser Pro Asp Ser
1 5 10 15
Leu Thr Ile Thr Cys Asn Tyr Gly Asn Gly Gly Cys Gln His Ser Cys
20 25 30
Glu Asp Thr Asp Thr Gly Pro Thr Cys Gly Cys His Gln Lys Tyr Ala
35 40 45
Leu His Ser Asp Gly Arg Thr Cys Ile Glu Lys Asp Glu Ala Ala Ile
50 55 60
Glu Arg Ser Gln Phe Asn Ala Thr Ser Val Ala Asp Val Asp Lys Arg
65 70 75 80
Val Lys Arg Arg Leu Leu Met Ala Pro Pro Asp Trp Gly Gln Lys Leu
85 90 95
Gly Leu Phe Gln Leu Gly Ala Pro Pro Gln Gly Thr Ala Gln Gly Leu
100 105 110
Ala Gln Ser Gly Ser Met Glu Ser Leu Leu Ile Asn Leu Val Ile Glu
115 120 125
His Asn Ser Leu Asp Thr Ser Ala Val Leu Val Thr Leu Thr Leu Pro
130 135 140
Cys Pro Asp Ser Val Trp Ser Val Gly Glu Ala Ser Ala His Thr Asp
145 150 155 160
Ser Ala Ala Leu Trp Gly Arg Ser Pro Gly Val Ser Ala Leu Pro Thr
165 170 175
Ser Trp Arg Arg Lys Pro Gly His Gln Arg Val Gln Thr Ser Arg Pro
180 185 190
Arg Arg Leu Ser Arg Pro Pro Gln Val Cys Phe Arg Val Gly Glu Ile
195 200 205
Pro His Glu Ala Ile Met Ser Ala Pro Glu Thr Cys Ala Val Asn Asn
210 215 220
Gly Gly Cys Asp Arg Thr Cys Lys Asp Thr Ala Thr Gly Val Arg Cys

225                      230                      235                      240  
 Ser Cys Pro Val Gly Phe Thr Leu Gln Pro Asp Gly Lys Thr Cys Lys  
                                  245                      250                      255  
 Asp Ile Asn Glu Cys Leu Val Asn Asn Gly Gly Cys Asp His Phe Cys  
                                  260                      265                      270  
 Arg Asn Thr Val Gly Ser Phe Glu Cys Gly Cys Arg Lys Gly Tyr Lys  
                                  275                      280                      285  
 Leu Leu Thr Asp Glu Arg Thr Cys Gln Asp Ile Asp Glu Cys Ser Phe  
                                  290                      295                      300  
 Glu Arg Thr Cys Asp His Ile Cys Ile Asn Ser Pro Gly Ser Phe Gln  
 305                      310                      315                      320  
 Cys Leu Cys His Arg Gly Tyr Ile Leu Tyr Gly Thr Thr His Cys Gly  
                                  325                      330                      335  
 Asp Val Asp Glu Cys Ser Met Ser Asn Gly Ser Cys Asp Gln Gly Cys  
                                  340                      345                      350  
 Val Asn Thr Lys Gly Ser Tyr Glu Cys Val Cys Pro Pro Gly Arg Arg  
                                  355                      360                      365  
 Leu His Trp Asn Gly Lys Asp Cys Val Gly Arg Gly Ser Leu Leu Leu  
                                  370                      375                      380  
 Gly Tyr Gly  
 385

<210> 58  
 <211> 964  
 <212> PRT  
 <213> Homo sapiens

<400> 58  
 Met Gly Ala Ala Ala Val Arg Trp His Leu Cys Val Leu Leu Ala Leu  
 1                      5                      10                      15  
 Gly Thr Arg Gly Arg Leu Ala Gly Gly Ser Gly Leu Pro Gly Ser Val  
                                  20                      25                      30  
 Asp Val Asp Glu Cys Ser Glu Gly Thr Asp Asp Cys His Ile Asp Ala  
                                  35                      40                      45  
 Ile Cys Gln Asn Thr Pro Lys Ser Tyr Lys Cys Leu Cys Lys Pro Gly  
 50                      55                      60  
 Tyr Lys Gly Glu Gly Lys Gln Cys Glu Asp Ile Asp Glu Cys Glu Asn  
 65                      70                      75                      80  
 Asp Tyr Tyr Asn Gly Gly Cys Val His Glu Cys Ile Asn Ile Pro Gly  
                                  85                      90                      95  
 Asn Tyr Arg Cys Thr Cys Phe Asp Gly Phe Met Leu Ala His Asp Gly  
                                  100                      105                      110  
 His Asn Cys Leu Asp Val Asp Glu Cys Gln Asp Asn Asn Gly Gly Cys  
                                  115                      120                      125  
 Gln Gln Ile Cys Val Asn Ala Met Gly Ser Tyr Glu Cys Gln Cys His  
 130                      135                      140  
 Ser Gly Phe Phe Leu Ser Asp Asn Gln His Thr Cys Ile His Arg Ser  
 145                      150                      155                      160  
 Asn Glu Gly Met Asn Cys Met Asn Lys Asp His Gly Cys Ala His Ile  
                                  165                      170                      175  
 Cys Arg Glu Thr Pro Lys Gly Gly Val Ala Cys Asp Cys Arg Pro Gly  
                                  180                      185                      190  
 Phe Asp Leu Ala Gln Asn Gln Lys Asp Cys Thr Leu Thr Cys Asn Tyr  
                                  195                      200                      205  
 Gly Asn Gly Gly Cys Gln His Ser Cys Glu Asp Thr Asp Thr Gly Pro  
 210                      215                      220  
 Thr Cys Gly Cys His Gln Lys Tyr Ala Leu His Ser Asp Gly Arg Thr  
 225                      230                      235                      240  
 Cys Ile Glu Thr Cys Ala Val Asn Asn Gly Gly Cys Asp Arg Thr Cys

				245					250				255				
Lys	Asp	Thr	Ala	Thr	Gly	Val	Arg	Cys	Ser	Cys	Pro	Val	Gly	Phe	Thr		
			260					265					270				
Leu	Gln	Pro	Asp	Gly	Lys	Thr	Cys	Lys	Asp	Ile	Asn	Glu	Cys	Leu	Val		
		275					280					285					
Asn	Asn	Gly	Gly	Cys	Asp	His	Phe	Cys	Arg	Asn	Thr	Val	Gly	Ser	Phe		
	290					295					300						
Glu	Cys	Gly	Cys	Arg	Lys	Gly	Tyr	Lys	Leu	Leu	Thr	Asp	Glu	Arg	Thr		
305					310					315					320		
Cys	Gln	Asp	Ile	Asp	Glu	Cys	Ser	Phe	Glu	Arg	Thr	Cys	Asp	His	Ile		
			325						330					335			
Cys	Ile	Asn	Ser	Pro	Gly	Ser	Phe	Gln	Cys	Leu	Cys	His	Arg	Gly	Tyr		
		340						345					350				
Ile	Leu	Tyr	Gly	Thr	Thr	His	Cys	Gly	Asp	Val	Asp	Glu	Cys	Ser	Met		
	355						360					365					
Ser	Asn	Gly	Ser	Cys	Asp	Gln	Gly	Cys	Val	Asn	Thr	Lys	Gly	Ser	Tyr		
	370					375					380						
Glu	Cys	Val	Cys	Pro	Pro	Gly	Arg	Arg	Leu	His	Trp	Asn	Gly	Lys	Asp		
385					390					395					400		
Cys	Val	Glu	Thr	Gly	Lys	Cys	Leu	Ser	Arg	Ala	Lys	Thr	Ser	Pro	Arg		
			405						410					415			
Ala	Gln	Leu	Ser	Cys	Ser	Lys	Ala	Gly	Gly	Val	Glu	Ser	Cys	Phe	Leu		
		420					425						430				
Ser	Cys	Pro	Ala	His	Thr	Leu	Phe	Val	Pro	Asp	Ser	Glu	Asn	Ser	Tyr		
	435						440					445					
Val	Leu	Ser	Cys	Gly	Val	Pro	Gly	Pro	Gln	Gly	Lys	Ala	Leu	Gln	Lys		
	450					455					460						
Arg	Asn	Gly	Thr	Ser	Ser	Gly	Leu	Gly	Pro	Ser	Cys	Ser	Asp	Ala	Pro		
465					470					475					480		
Thr	Thr	Pro	Ile	Lys	Gln	Lys	Ala	Arg	Phe	Lys	Ile	Arg	Asp	Ala	Lys		
			485						490					495			
Cys	His	Leu	Arg	Pro	His	Ser	Gln	Ala	Arg	Ala	Lys	Glu	Thr	Ala	Arg		
		500						505					510				
Gln	Pro	Leu	Leu	Asp	His	Cys	His	Val	Thr	Phe	Val	Thr	Leu	Lys	Cys		
	515						520					525					
Asp	Ser	Ser	Lys	Lys	Arg	Arg	Gly	Arg	Lys	Ser	Pro	Ser	Lys	Glu			
	530					535				540							
Val	Ser	His	Ile	Thr	Ala	Glu	Phe	Glu	Ile	Glu	Thr	Lys	Met	Glu	Glu		
545					550					555					560		
Ala	Ser	Asp	Thr	Cys	Glu	Ala	Asp	Cys	Leu	Arg	Lys	Arg	Ala	Glu	Gln		
			565						570					575			
Ser	Leu	Gln	Ala	Ala	Ile	Lys	Thr	Leu	Arg	Lys	Ser	Ile	Gly	Arg	Gln		
		580						585					590				
Gln	Phe	Tyr	Val	Gln	Val	Ser	Gly	Thr	Glu	Tyr	Glu	Val	Ala	Gln	Arg		
	595						600					605					
Pro	Ala	Lys	Ala	Leu	Glu	Gly	Gln	Gly	Ala	Cys	Gly	Ala	Gly	Gln	Val		
	610					615					620						
Leu	Gln	Asp	Ser	Lys	Cys	Val	Ala	Cys	Gly	Pro	Gly	Thr	His	Phe	Gly		
625					630					635					640		
Gly	Glu	Leu	Gly	Gln	Cys	Val	Ser	Cys	Met	Pro	Gly	Thr	Tyr	Gln	Asp		
			645						650					655			
Met	Glu	Gly	Gln	Leu	Ser	Cys	Thr	Pro	Cys	Pro	Ser	Ser	Asp	Gly	Leu		
		660						665					670				
Gly	Leu	Pro	Gly	Ala	Arg	Asn	Val	Ser	Glu	Cys	Gly	Gly	Gln	Cys	Ser		
	675						680					685					
Pro	Gly	Phe	Phe	Ser	Ala	Asp	Gly	Phe	Lys	Pro	Cys	Gln	Ala	Cys	Pro		
	690					695					700						
Val	Gly	Thr	Tyr	Gln	Pro	Glu	Pro	Gly	Arg	Thr	Gly	Cys	Phe	Pro	Cys		
705					710					715					720		

Gly Gly Gly Leu Leu Thr Lys His Glu Gly Thr Thr Ser Phe Gln Asp  
                               725                              730                              735  
 Cys Glu Ala Lys Val His Cys Ser Pro Gly His His Tyr Asn Thr Thr  
                               740                              745                              750  
 Thr His Arg Cys Ile Arg Cys Pro Val Gly Thr Tyr Gln Pro Glu Phe  
                               755                              760                              765  
 Gly Gln Asn His Cys Ile Thr Cys Pro Gly Asn Thr Ser Thr Asp Phe  
                               770                              775                              780  
 Asp Gly Ser Thr Asn Val Thr His Cys Lys Asn Gln His Cys Gly Gly  
                               785                              790                              795                              800  
 Glu Leu Gly Asp Tyr Thr Gly Tyr Ile Glu Ser Pro Asn Tyr Pro Gly  
                               805                              810                              815  
 Asp Tyr Pro Ala Asn Ala Glu Cys Val Trp His Ile Ala Pro Pro Pro  
                               820                              825                              830  
 Lys Arg Arg Ile Leu Ile Val Val Pro Glu Ile Phe Leu Pro Ile Glu  
                               835                              840                              845  
 Asp Glu Cys Gly Asp Val Leu Val Met Arg Lys Ser Ala Ser Pro Thr  
                               850                              855                              860  
 Ser Ile Thr Thr Tyr Glu Thr Cys Gln Thr Tyr Glu Arg Pro Ile Ala  
                               865                              870                              875                              880  
 Phe Thr Ser Arg Ser Arg Lys Leu Trp Ile Gln Phe Lys Ser Asn Glu  
                               885                              890                              895  
 Gly Asn Ser Gly Lys Gly Phe Gln Val Pro Tyr Val Thr Tyr Asp Gly  
                               900                              905                              910  
 Lys Ile His Cys Leu His Gly Pro Leu Cys Thr Ala Gln Ala Gly Pro  
                               915                              920                              925  
 Trp Arg His Arg Asp Glu Ser His Val Pro Ala Leu Arg Glu Leu Arg  
                               930                              935                              940  
 Pro Gly Arg Tyr Arg Pro Gly Ser Arg Thr Asn Thr Val Arg Gly Gln  
                               945                              950                              955                              960  
 Ser Gln Thr Gly

<210> 59  
 <211> 213  
 <212> PRT  
 <213> Homo sapiens

<400> 59  
 Ala Met Val Leu Pro Ser Tyr Ser Lys Ser Glu Gly Gly Ser Leu Leu  
   1                              5                              10                              15  
 Asp Ile Tyr Cys Leu Leu Thr Tyr Trp Met Glu Val Val Pro Thr Leu  
                               20                              25                              30  
 Leu Ala Glu Thr Lys Ile Pro Ala Thr Asp Val Ala Asp Ala Ser Leu  
                               35                              40                              45  
 Asn Glu Cys Ser Ser Thr Glu Arg Lys Gln Asp Val Val Leu Leu Phe  
                               50                              55                              60  
 Val Thr Leu Ser His Thr Gln Pro Pro Leu Phe His Leu Pro Tyr Val  
                               65                              70                              75                              80  
 Gln Lys Pro Leu Ile Ser Asn Val Glu Gln Leu Ile Leu Gly Ile Pro  
                               85                              90                              95  
 Gly Gln Asn Arg Arg Glu Ile Gly His Gly Gln Asp Ile Phe Pro Ala  
                               100                              105                              110  
 Glu Lys Leu Cys His Leu Gln Asp Arg Lys Val Asn Leu His Arg Ala  
                               115                              120                              125  
 Ala Trp Gly Glu Cys Ile Val Ala Pro Lys Thr Leu Ser Phe Ser Tyr  
                               130                              135                              140  
 Cys Gln Gly Thr Cys Pro Ala Leu Asn Ser Glu Leu Arg His Ser Ser  
                               145                              150                              155                              160



Phe Glu Cys Tyr Lys Arg Ala Val Pro Thr Cys Pro Trp Leu Phe Gln  
 165 170 175  
 Thr Cys Arg Pro Thr Met Val Arg Leu Phe Ser Leu Met Val Gln Asp  
 180 185 190  
 Asp Glu His Lys Met Ser Val His Tyr Val Asn Thr Ser Leu Val Glu  
 195 200 205  
 Lys Cys Gly Cys Ser  
 210

<210> 60  
 <211> 189  
 <212> PRT  
 <213> Homo sapiens

<400> 60  
 Asx Met Glu Val Val Pro Thr Leu Leu Ala Glu Thr Lys Ile Pro Ala  
 1 5 10 15  
 Thr Asp Val Ala Asp Ala Ser Leu Asn Glu Cys Ser Ser Thr Glu Arg  
 20 25 30  
 Lys Gln Asp Val Val Leu Leu Phe Val Thr Leu Ser His Thr Gln Pro  
 35 40 45  
 Pro Leu Phe His Leu Pro Tyr Val Gln Lys Pro Leu Ile Ser Asn Val  
 50 55 60  
 Glu Gln Leu Ile Leu Gly Ile Pro Gly Gln Asn Arg Arg Glu Ile Gly  
 65 70 75 80  
 His Gly Gln Asp Ile Phe Pro Ala Glu Lys Leu Cys His Leu Gln Asp  
 85 90 95  
 Arg Lys Val Asn Leu His Arg Ala Ala Trp Gly Glu Cys Ile Val Ala  
 100 105 110  
 Pro Lys Thr Leu Ser Phe Ser Tyr Cys Gln Gly Thr Cys Pro Ala Leu  
 115 120 125  
 Asn Ser Glu Leu Arg His Ser Ser Phe Glu Cys Tyr Lys Arg Ala Val  
 130 135 140  
 Pro Thr Cys Pro Trp Leu Phe Gln Thr Cys Arg Pro Thr Met Val Arg  
 145 150 155 160  
 Leu Phe Ser Leu Met Val Gln Asp Asp Glu His Lys Met Ser Val His  
 165 170 175  
 Tyr Val Asn Thr Ser Leu Val Glu Lys Cys Gly Cys Ser  
 180 185

<210> 61  
 <211> 740  
 <212> PRT  
 <213> Homo sapiens

<400> 61  
 Met Gly Asp Ser Gly Ala Glu Ala Val Gly Gly Gly Gly Thr Tyr Thr  
 1 5 10 15  
 Asp Gly Pro Val Leu Leu Leu Tyr Ala Gly Glu Leu Leu Leu Pro Gln  
 20 25 30  
 Glu Thr Thr Val Glu Leu Ser Cys Gly Val Gly Pro Leu Gln Val Ile  
 35 40 45  
 Leu Gly Pro Glu Gln Ala Ala Val Leu Asn Cys Ser Leu Gly Ala Ala  
 50 55 60  
 Ala Ala Gly Pro Pro Thr Arg Val Thr Trp Ser Lys Asp Gly Asp Thr  
 65 70 75 80  
 Leu Leu Glu His Asp His Leu His Leu Leu Pro Asn Gly Ser Leu Trp  
 85 90 95  
 Leu Ser Gln Pro Leu Ala Pro Asn Gly Ser Asp Glu Ser Val Pro Glu

50/60

				100									110		
Ala Val Gly Val Ile Glu Gly Asn Tyr Ser Cys Leu Ala His Gly Pro															
		115					120					125			
Pro Gly Val Leu Ala Ser Gln Thr Ala Val Val Lys Leu Ala Thr Leu															
		130				135					140				
Ala Asp Phe Ser Leu His Pro Glu Ser Gln Thr Val Glu Glu Asn Gly					150					155					160
Thr Ala Arg Phe Glu Cys His Ile Glu Gly Leu Pro Ala Pro Ile Ile				165					170					175	
			Lys Asp Gln Val Thr Leu Pro Glu Glu Pro Arg Leu Ile												
Thr Trp Glu			180				185							190	
Val Leu Pro Asn Gly Val Leu Gln Ile Leu Asp Val Gln Glu Ser Asp															
		195				200						205			
Ala Gly Pro Tyr Arg Cys Val Ala Thr Asn Ser Ala Arg Gln His Phe															
		210				215					220				
Ser Gln Glu Ala Leu Leu Ser Val Ala His Arg Gly Ser Leu Ala Ser					230					235					240
Thr Arg Gly Gln Asp Val Val Ile Val Ala Ala Pro Glu Asn Thr Thr				245					250					255	
			Gly Gln Ser Val Val Met Glu Cys Val Ala Ser Ala Asp												
Val Val Ser			260				265						270		
			Phe Val Ser Trp Val Arg Gln Asp Gly Lys Pro Ile Ser												
Pro Thr Pro			275			280							285		
			Ile Val Leu Gly Arg Thr Asn Leu Leu Ile Ala Asn Ala												
Thr Asp Val			290			295					300				
			Trp His Ser Gly Val Tyr Val Cys Arg Ala Asn Lys Pro Arg												
Gln Pro			305			310				315					320
Thr Arg Asp				Ala Thr Ala Ala Ala Glu Leu Arg Val Leu Ala Ala											
				325					330					335	
Pro Ala Ile Thr Gln Ala Pro Glu Ala Leu Ser Arg Thr Arg Ala Ser															
			340				345						350		
Thr Ala Arg Phe Val Cys Arg Ala Ser Gly Glu Pro Arg Pro Ala Leu															
			355			360							365		
Arg Trp Leu His Asn Gly Ala Pro Leu Arg Pro Asn Gly Arg Val Lys						375					380				
			370												
Val Gln Gly Gly Gly Gly Ser Leu Val Ile Thr Gln Ile Gly Leu Gln					390					395					400
Asp Ala Gly Tyr Tyr Gln Cys Val Ala Glu Asn Ser Ala Gly Met Ala									410						
			405											415	
Cys Ala Ala Ala Ser Leu Ala Val Val Val Arg Glu Gly Leu Pro Ser															
			420				425						430		
Ala Pro Thr Arg Val Thr Ala Thr Pro Leu Ser Ser Ser Ala Val Leu															
			435				440						445		
Val Ala Trp Glu Arg Pro Glu Met His Ser Glu Gln Ile Ile Gly Phe															
			450			455							460		
Ser Leu His Tyr Gln Lys Ala Arg Gly Met Asp Asn Val Glu Tyr Gln															
			465			470				475					480
Phe Ala Val Asn Asn Asp Thr Thr Glu Leu Gln Val Arg Asp Leu Glu															
			485							490					495
Pro Asn Thr Asp Tyr Glu Phe Tyr Val Val Ala Tyr Ser Gln Leu Gly															
			500				505					</			

Leu Gln Pro Asn Lys Val Tyr Arg Val Arg Ile Ser Ala Gly Thr Ala  
 580 585 590  
 Ala Gly Phe Gly Ala Pro Ser Gln Trp Met His His Arg Thr Pro Ser  
 595 600 605  
 Met His Asn Gln Ser His Val Pro Phe Ala Pro Ala Glu Leu Lys Val  
 610 615 620  
 Gln Ala Lys Met Glu Ser Leu Val Val Ser Trp Gln Pro Pro Pro His  
 625 630 635 640  
 Pro Thr Gln Ile Ser Gly Tyr Lys Leu Tyr Trp Arg Glu Val Gly Ala  
 645 650 655  
 Glu Glu Glu Ala Asn Gly Asp Arg Leu Pro Gly Gly Arg Gly Asp Gln  
 660 665 670  
 Ala Trp Asp Val Gly Pro Val Arg Leu Lys Lys Lys Val Lys Gln Tyr  
 675 680 685  
 Glu Leu Thr Gln Leu Val Pro Gly Arg Leu Tyr Glu Val Lys Leu Val  
 690 695 700  
 Ala Phe Asn Lys His Glu Asp Gly Tyr Ala Ala Val Trp Lys Gly Lys  
 705 710 715 720  
 Thr Glu Lys Ala Pro Ala Pro Gly Glu Gly Gly Gly Arg Arg Arg  
 725 730 735  
 Gly Gly Leu Arg  
 740

<210> 62  
 <211> 1250  
 <212> PRT  
 <213> Homo sapiens

<400> 62  
 Met Ala Arg Gly Asp Ala Gly Arg Gly Arg Gly Leu Leu Ala Leu Thr  
 1 5 10 15  
 Phe Cys Leu Leu Ala Ala Arg Gly Glu Leu Leu Leu Pro Gln Glu Thr  
 20 25 30  
 Thr Val Glu Leu Ser Cys Gly Val Gly Pro Leu Gln Val Ile Leu Gly  
 35 40 45  
 Pro Glu Gln Ala Ala Val Leu Asn Cys Ser Leu Gly Ala Ala Ala Ala  
 50 55 60  
 Gly Pro Pro Thr Arg Val Thr Trp Ser Lys Asp Gly Asp Thr Leu Leu  
 65 70 75 80  
 Glu His Asp His Leu His Leu Leu Pro Asn Gly Ser Leu Trp Leu Ser  
 85 90 95  
 Gln Pro Leu Ala Pro Asn Gly Ser Asp Glu Ser Val Pro Glu Ala Val  
 100 105 110  
 Gly Val Ile Glu Gly Asn Tyr Ser Cys Leu Ala His Gly Pro Leu Gly  
 115 120 125  
 Val Leu Ala Ser Gln Thr Ala Val Val Lys Leu Ala Thr Leu Ala Asp  
 130 135 140  
 Phe Ser Leu His Pro Glu Ser Gln Thr Val Glu Glu Asn Gly Thr Ala  
 145 150 155 160  
 Arg Phe Glu Cys His Ile Glu Gly Leu Pro Ala Pro Ile Ile Thr Trp  
 165 170 175  
 Glu Lys Asp Gln Val Thr Leu Pro Glu Glu Pro Arg Leu Ile Val Leu  
 180 185 190  
 Pro Asn Gly Val Leu Gln Ile Leu Asp Val Gln Glu Ser Asp Ala Gly  
 195 200 205  
 Pro Tyr Arg Cys Val Ala Thr Asn Ser Ala Arg Gln His Phe Ser Gln  
 210 215 220  
 Glu Ala Leu Leu Ser Val Ala His Arg Gly Ser Leu Ala Ser Thr Arg  
 225 230 235 240

Gly Gln Asp Val Val Ile Val Ala Ala Pro Glu Asn Thr Thr Val Val  
 245 250 255  
 Ser Gly Gln Ser Val Val Met Glu Cys Val Ala Ser Ala Asp Pro Thr  
 260 265 270  
 Pro Phe Val Ser Trp Val Arg Gln Asp Gly Lys Pro Ile Ser Thr Asp  
 275 280 285  
 Val Ile Val Leu Gly Arg Thr Asn Leu Leu Ile Ala Asn Ala Gln Pro  
 290 295 300  
 Trp His Ser Gly Val Tyr Val Cys Arg Ala Asn Lys Pro Arg Thr Arg  
 305 310 315 320  
 Asp Phe Ala Thr Ala Ala Ala Glu Leu Arg Val Leu Ala Ala Pro Ala  
 325 330 335  
 Ile Thr Gln Ala Pro Glu Ala Leu Ser Arg Thr Arg Ala Ser Thr Ala  
 340 345 350  
 Arg Phe Val Cys Arg Ala Ser Gly Glu Pro Arg Pro Ala Leu Arg Trp  
 355 360 365  
 Leu His Asn Gly Ala Pro Leu Arg Pro Asn Gly Arg Val Lys Val Gln  
 370 375 380  
 Gly Gly Gly Gly Ser Leu Val Ile Thr Gln Ile Gly Leu Gln Asp Ala  
 385 390 395 400  
 Gly Tyr Tyr Gln Cys Val Ala Glu Asn Ser Ala Gly Met Ala Cys Ala  
 405 410 415  
 Ala Ala Ser Leu Ala Val Val Val Arg Glu Gly Leu Pro Ser Ala Pro  
 420 425 430  
 Thr Arg Val Thr Ala Thr Pro Leu Ser Ser Ser Ala Val Leu Val Ala  
 435 440 445  
 Trp Glu Arg Pro Glu Met His Ser Glu Gln Ile Ile Gly Phe Ser Leu  
 450 455 460  
 His Tyr Gln Lys Ala Arg Gly Met Asp Asn Val Glu Tyr Gln Phe Ala  
 465 470 475 480  
 Val Asn Asn Asp Thr Thr Glu Leu Gln Val Arg Asp Leu Glu Pro Asn  
 485 490 495  
 Thr Asp Tyr Glu Phe Tyr Val Val Ala Tyr Ser Gln Leu Gly Ala Ser  
 500 505 510  
 Arg Thr Ser Thr Pro Ala Leu Val His Thr Leu Asp Asp Val Pro Ser  
 515 520 525  
 Ala Ala Pro Gln Leu Ser Leu Ser Ser Pro Asn Pro Ser Asp Ile Arg  
 530 535 540  
 Val Ala Trp Leu Pro Leu Pro Pro Ser Leu Ser Asn Gly Gln Val Val  
 545 550 555 560  
 Lys Tyr Lys Ile Glu Tyr Gly Leu Gly Lys Glu Asp Gln Ile Phe Ser  
 565 570 575  
 Thr Glu Val Arg Gly Asn Glu Thr Gln Leu Met Leu Asn Ser Leu Gln  
 580 585 590  
 Pro Asn Lys Val Tyr Arg Val Arg Ile Ser Ala Gly Thr Ala Ala Gly  
 595 600 605  
 Phe Gly Ala Pro Ser Gln Trp Met His His Arg Thr Pro Ser Met His  
 610 615 620  
 Asn Gln Ser His Val Pro Phe Ala Pro Ala Glu Leu Lys Val Gln Ala  
 625 630 635 640  
 Lys Met Glu Ser Leu Val Val Ser Trp Gln Pro Pro Pro His Pro Thr  
 645 650 655  
 Gln Ile Ser Gly Tyr Lys Leu Tyr Trp Arg Glu Val Gly Ala Glu Glu  
 660 665 670  
 Glu Ala Asn Gly Asp Arg Leu Pro Gly Gly Arg Gly Asp Gln Ala Trp  
 675 680 685  
 Asp Val Gly Pro Val Arg Leu Lys Lys Lys Val Lys Gln Tyr Glu Leu  
 690 695 700  
 Thr Gln Leu Val Pro Gly Arg Leu Tyr Glu Val Lys Leu Val Ala Phe

705		710		715		720
Asn Lys His Glu Asp Gly Tyr Ala Ala Val Trp Lys Gly Lys Thr Glu						
	725			730		735
Lys Ala Pro Ala Pro Asp Met Pro Ile Gln Arg Gly Pro Pro Leu Pro						
	740			745		750
Pro Ala His Val His Ala Glu Ser Asn Ser Ser Thr Ser Ile Trp Leu						
	755			760		765
Arg Trp Lys Lys Pro Asp Phe Thr Thr Val Lys Ile Val Asn Tyr Thr						
	770			775		780
Val Arg Phe Ser Pro Trp Gly Leu Arg Asn Ala Ser Leu Val Thr Tyr						
	785			790		795
Tyr Thr Ser Ser Gly Glu Asp Ile Leu Ile Gly Gly Leu Lys Pro Phe						
	805			810		815
Thr Lys Tyr Glu Phe Ala Val Gln Ser His Gly Val Asp Met Asp Gly						
	820			825		830
Pro Phe Gly Ser Val Val Glu Arg Ser Thr Leu Pro Asp Arg Pro Ser						
	835			840		845
Thr Pro Pro Ser Asp Leu Arg Leu Ser Pro Leu Thr Pro Ser Thr Val						
	850			855		860
Arg Leu His Trp Cys Pro Pro Thr Glu Pro Asn Gly Glu Ile Val Glu						
	865			870		875
Tyr Leu Ile Leu Tyr Ser Ser Asn His Thr Gln Pro Glu His Gln Trp						
	885			890		895
Thr Leu Leu Thr Thr Gln Gly Asn Ile Phe Ser Ala Glu Val His Gly						
	900			905		910
Leu Glu Ser Asp Thr Arg Tyr Phe Phe Lys Met Gly Ala Arg Thr Glu						
	915			920		925
Val Gly Pro Gly Pro Phe Ser Arg Leu Gln Asp Val Ile Thr Leu Gln						
	930			935		940
Glu Lys Leu Ser Asp Ser Leu Asp Met His Ser Val Thr Gly Ile Ile						
	945			950		955
Val Gly Val Cys Leu Gly Leu Leu Cys Leu Leu Ala Cys Met Cys Ala						
	965			970		975
Gly Leu Arg Arg Ser Pro His Arg Glu Ser Leu Pro Gly Leu Ser Ser						
	980			985		990
Thr Ala Thr Pro Gly Asn Pro Ala Leu Tyr Ser Arg Ala Arg Leu Gly						
	995			1000		1005
Pro Pro Ser Pro Pro Ala Ala His Glu Leu Glu Ser Leu Val His Pro						
	1010			1015		1020
His Pro Gln Asp Trp Ser Pro Pro Pro Ser Asp Val Glu Asp Arg Ala						
	1025			1030		1035
Glu Val His Ser Leu Met Gly Gly Gly Val Ser Glu Gly Arg Ser His						
	1045			1050		1055
Ser Lys Arg Lys Ile Ser Trp Ala Gln Pro Ser Gly Leu Ser Trp Ala						
	1060			1065		1070
Gly Ser Trp Ala Gly Cys Glu Leu Pro Gln Ala Gly Pro Arg Pro Ala						
	1075			1080		1085
Leu Thr Arg Ala Leu Leu Pro Pro Ala Gly Thr Gly Gln Thr Leu Leu						
	1090			1095		1100
Leu Gln Ala Leu Val Tyr Asp Ala Ile Lys Gly Asn Gly Arg Lys Lys						
	1105			1110		1115
Ser Pro Pro Ala Cys Arg Asn Gln Val Glu Ala Glu Val Ile Val His						
	1125			1130		1135
Ser Asp Phe Ser Ala Ser Asn Gly Asn Pro Asp Leu His Leu Gln Asp						
	1140			1145		1150
Leu Glu Pro Glu Asp Pro Leu Pro Pro Glu Ala Pro Asp Leu Ile Ser						
	1155			1160		1165
Gly Val Gly Asp Pro Gly Gln Gly Ala Ala Trp Leu Asp Arg Glu Leu						
	1170			1175		1180

Gly Gly Cys Glu Leu Ala Ala Pro Gly Pro Asp Arg Leu Thr Cys Leu  
 1185 1190 1195 1200  
 Pro Glu Ala Ala Ser Ala Ser Cys Ser Tyr Pro Asp Leu Gln Pro Gly  
 1205 1210 1215  
 Glu Val Leu Glu Glu Thr Pro Gly Asp Ser Cys Gln Leu Lys Ser Pro  
 1220 1225 1230  
 Cys Pro Leu Gly Ala Ser Pro Gly Leu Pro Arg Ser Pro Val Ser Ser  
 1235 1240 1245  
 Ser Ala  
 1250

<210> 63  
 <211> 634  
 <212> PRT  
 <213> Homo sapiens

<400> 63  
 Met Ala Gln Gly Val Leu Trp Ile Leu Leu Gly Leu Leu Leu Trp Ser  
 1 5 10 15  
 Asp Pro Gly Thr Ala Ser Leu Pro Leu Leu Met Asp Ser Val Ile Gln  
 20 25 30  
 Ala Leu Ala Glu Leu Glu Gln Lys Val Pro Ala Ala Lys Thr Arg His  
 35 40 45  
 Thr Ala Ser Ala Trp Leu Met Ser Ala Pro Asn Ser Gly Pro His Asn  
 50 55 60  
 Arg Leu Tyr His Phe Leu Leu Gly Ala Trp Ser Leu Asn Ala Thr Glu  
 65 70 75 80  
 Leu Asp Pro Cys Pro Leu Ser Pro Glu Leu Leu Gly Leu Thr Lys Glu  
 85 90 95  
 Val Ala Arg His Asp Val Arg Glu Gly Lys Glu Tyr Gly Val Val Leu  
 100 105 110  
 Ala Pro Asp Gly Ser Thr Val Ala Val Glu Pro Leu Leu Ala Gly Leu  
 115 120 125  
 Glu Ala Gly Leu Gln Gly Arg Arg Val Ile Asn Leu Pro Leu Asp Ser  
 130 135 140  
 Met Ala Ala Pro Trp Glu Thr Gly Asp Thr Phe Pro Asp Val Val Ala  
 145 150 155 160  
 Ile Ala Pro Asp Val Arg Ala Thr Ser Ser Pro Gly Leu Arg Asp Gly  
 165 170 175  
 Ser Pro Asp Val Thr Thr Ala Asp Ile Gly Ala Asn Thr Pro Asp Ala  
 180 185 190  
 Thr Lys Gly Cys Pro Asp Val Gln Ala Ser Leu Pro Asp Ala Lys Ala  
 195 200 205  
 Lys Ser Pro Pro Thr Met Val Asp Ser Leu Leu Ala Val Thr Leu Ala  
 210 215 220  
 Gly Asn Leu Gly Leu Thr Phe Leu Arg Gly Ser Gln Thr Gln Ser His  
 225 230 235 240  
 Pro Asp Leu Gly Thr Glu Gly Cys Trp Asp Gln Leu Ser Ala Pro Arg  
 245 250 255  
 Thr Phe Thr Leu Leu Asp Pro Lys Ala Ser Leu Leu Thr Met Ala Phe  
 260 265 270  
 Leu Asn Gly Ala Leu Asp Gly Val Ile Leu Gly Asp Tyr Leu Ser Arg  
 275 280 285  
 Thr Pro Glu Pro Arg Pro Ser Leu Ser His Leu Leu Ser Gln Tyr Tyr  
 290 295 300  
 Gly Ala Gly Val Ala Arg Asp Pro Gly Phe Arg Ser Asn Phe Arg Arg  
 305 310 315 320  
 Gln Asn Gly Ala Ala Leu Thr Ser Ala Ser Ile Leu Ala Gln Gln Val  
 325 330 335

Trp Gly Thr Leu Val Leu Leu Gln Arg Leu Glu Pro Val His Leu Gln  
 340 345 350  
 Leu Gln Cys Met Ser Gln Glu Gln Leu Ala Gln Val Ala Ala Asn Ala  
 355 360 365  
 Thr Lys Glu Phe Thr Glu Ala Phe Leu Gly Cys Pro Ala Ile His Pro  
 370 375 380  
 Arg Cys Arg Trp Gly Ala Ala Pro Tyr Arg Gly Arg Pro Lys Leu Leu  
 385 390 395 400  
 Gln Leu Pro Leu Gly Phe Leu Tyr Val His His Thr Tyr Val Pro Ala  
 405 410 415  
 Pro Pro Cys Thr Asp Phe Thr Arg Cys Ala Ala Asn Met Arg Ser Met  
 420 425 430  
 Gln Arg Tyr His Gln Asp Thr Gln Gly Trp Gly Asp Ile Gly Tyr Ser  
 435 440 445  
 Phe Val Val Gly Ser Asp Gly Tyr Val Tyr Glu Gly Arg Gly Trp His  
 450 455 460  
 Trp Val Gly Ala His Thr Leu Gly His Asn Ser Arg Gly Phe Gly Val  
 465 470 475 480  
 Ala Ile Val Gly Asn Tyr Thr Ala Ala Leu Pro Thr Glu Ala Ala Leu  
 485 490 495  
 Arg Thr Val Arg Asp Thr Leu Pro Ser Cys Ala Val Arg Ala Gly Leu  
 500 505 510  
 Leu Arg Pro Asp Tyr Ala Leu Leu Gly His Arg Gln Leu Val Arg Thr  
 515 520 525  
 Asp Cys Pro Gly Asp Ala Leu Phe Asp Leu Leu Arg Thr Trp Pro His  
 530 535 540  
 Phe Thr Ala Val Ser Leu Arg Ser Leu His Tyr Thr Ala Arg Arg Pro  
 545 550 555 560  
 Ser Val Tyr Thr Ser Ser Thr Arg Pro Leu Pro Pro Ala Cys Asn Ser  
 565 570 575  
 Cys Ala Arg Thr Ala Ser Ala Arg Pro Pro Thr Ser Arg Arg His Val  
 580 585 590  
 Tyr Ser Gly Asn Leu Gly Pro Ala Phe Ala Gly His Ser Ala Gly Asn  
 595 600 605  
 Ile Pro Asp Pro Val Thr Ser Ala Tyr Ala Ala Ser Ala Gln Pro Gln  
 610 615 620  
 Thr Gln Pro Ala Cys Pro Phe Pro Ser Ser  
 625 630

<210> 64  
 <211> 576  
 <212> PRT  
 <213> Homo sapiens

<400> 64  
 Met Ala Gln Gly Val Leu Trp Ile Leu Leu Gly Leu Leu Leu Trp Ser  
 1 5 10 15  
 Asp Pro Gly Thr Ala Ser Leu Pro Leu Leu Met Asp Ser Val Ile Gln  
 20 25 30  
 Ala Leu Ala Glu Leu Glu Gln Lys Val Pro Ala Ala Lys Thr Arg His  
 35 40 45  
 Thr Ala Ser Ala Trp Leu Met Ser Ala Pro Asn Ser Gly Pro His Asn  
 50 55 60  
 Arg Leu Tyr His Phe Leu Leu Gly Ala Trp Ser Leu Asn Ala Thr Glu  
 65 70 75 80  
 Leu Asp Pro Cys Pro Leu Ser Pro Glu Leu Leu Gly Leu Thr Lys Glu  
 85 90 95  
 Val Ala Arg His Asp Val Arg Glu Gly Lys Glu Tyr Gly Val Val Leu  
 100 105 110

56/60

Ala	Pro	Asp	Gly	Ser	Thr	Val	Ala	Val	Glu	Pro	Leu	Leu	Ala	Gly	Leu
		115					120					125			
Glu	Ala	Gly	Leu	Gln	Gly	Arg	Arg	Val	Ile	Asn	Leu	Pro	Leu	Asp	Ser
		130				135					140				
Met	Ala	Ala	Pro	Trp	Glu	Thr	Gly	Asp	Thr	Phe	Pro	Asp	Val	Val	Ala
145					150					155					160
Ile	Ala	Pro	Asp	Val	Arg	Ala	Thr	Ser	Ser	Pro	Gly	Leu	Arg	Asp	Gly
				165					170					175	
Ser	Pro	Asp	Val	Thr	Thr	Ala	Asp	Ile	Gly	Ala	Asn	Thr	Pro	Asp	Ala
			180					185					190		
Thr	Lys	Gly	Cys	Pro	Asp	Val	Gln	Ala	Ser	Leu	Pro	Asp	Ala	Lys	Ala
		195					200					205			
Lys	Ser	Pro	Pro	Thr	Met	Val	Asp	Ser	Leu	Leu	Ala	Val	Thr	Leu	Ala
		210				215					220				
Gly	Asn	Leu	Gly	Leu	Thr	Phe	Leu	Arg	Gly	Ser	Gln	Thr	Gln	Ser	His
225					230					235					240
Pro	Asp	Leu	Gly	Thr	Glu	Gly	Cys	Trp	Asp	Gln	Leu	Ser	Ala	Pro	Arg
				245					250					255	
Thr	Phe	Thr	Leu	Leu	Asp	Pro	Lys	Ala	Ser	Leu	Leu	Thr	Met	Ala	Phe
			260					265						270	
Leu	Asn	Gly	Ala	Leu	Asp	Gly	Val	Ile	Leu	Gly	Asp	Tyr	Leu	Ser	Arg
		275					280					285			
Thr	Pro	Glu	Pro	Arg	Pro	Ser	Leu	Ser	His	Leu	Leu	Ser	Gln	Tyr	Tyr
		290				295					300				
Gly	Ala	Gly	Val	Ala	Arg	Asp	Pro	Gly	Phe	Arg	Ser	Asn	Phe	Arg	Arg
305					310					315					320
Gln	Asn	Gly	Ala	Ala	Leu	Thr	Ser	Ala	Ser	Ile	Leu	Ala	Gln	Gln	Val
				325					330					335	
Trp	Gly	Thr	Leu	Val	Leu	Leu	Gln	Arg	Leu	Glu	Pro	Val	His	Leu	Gln
			340					345					350		
Leu	Gln	Cys	Met	Ser	Gln	Glu	Gln	Leu	Ala	Gln	Val	Ala	Ala	Asn	Ala
		355					360					365			
Thr	Lys	Glu	Phe	Thr	Glu	Ala	Phe	Leu	Gly	Cys	Pro	Ala	Ile	His	Pro
		370				375					380				
Arg	Cys	Arg	Trp	Gly	Ala	Ala	Pro	Tyr	Arg	Gly	Arg	Pro	Lys	Leu	Leu
385					390					395					400
Gln	Leu	Pro	Leu	Gly	Phe	Leu	Tyr	Val	His	His	Thr	Tyr	Val	Pro	Ala
				405					410					415	
Pro	Pro	Cys	Thr	Asp	Phe	Thr	Arg	Cys	Ala	Ala	Asn	Met	Arg	Ser	Met
			420					425				430			
Gln	Arg	Tyr	His	Gln	Asp	Thr	Gln	Gly	Trp	Gly	Asp	Ile	Gly	Tyr	Ser
		435					440					445			
Phe	Val	Val	Gly	Ser	Asp	Gly	Tyr	Val	Tyr	Glu	Gly	Arg	Gly	Trp	His
		450				455					460				



<210> 65  
 <211> 734  
 <212> PRT  
 <213> Homo sapiens

<400> 65  
 Met Trp Gly Leu Leu Leu Ala Leu Ala Ala Phe Ala Pro Ala Val Gly  
 1 5 10 15  
 Pro Ala Leu Gly Ala Pro Arg Asn Ser Val Leu Gly Leu Ala Gln Pro  
 20 25 30  
 Gly Thr Thr Lys Val Pro Gly Ser Thr Pro Ala Leu His Ser Ser Pro  
 35 40 45  
 Ala Gln Pro Pro Ala Glu Thr Ala Asn Gly Thr Ser Glu Gln His Val  
 50 55 60  
 Arg Ile Arg Val Ile Lys Lys Lys Lys Val Ile Met Lys Lys Arg Lys  
 65 70 75 80  
 Lys Leu Thr Leu Thr Arg Pro Thr Pro Leu Val Thr Ala Gly Pro Leu  
 85 90 95  
 Val Thr Pro Thr Pro Ala Gly Thr Leu Asp Pro Ala Glu Lys Gln Glu  
 100 105 110  
 Thr Gly Cys Pro Pro Leu Gly Leu Glu Ser Leu Arg Val Ser Asp Ser  
 115 120 125  
 Arg Leu Glu Ala Ser Ser Ser Gln Ser Phe Gly Leu Gly Pro His Arg  
 130 135 140  
 Gly Arg Leu Asn Ile Gln Ser Gly Leu Glu Asp Gly Asp Leu Tyr Asp  
 145 150 155 160  
 Gly Ala Trp Cys Ala Glu Glu Gln Asp Ala Asp Pro Trp Phe Gln Val  
 165 170 175  
 Asp Ala Gly His Pro Thr Arg Phe Ser Gly Val Ile Thr Gln Gly Arg  
 180 185 190  
 Asn Ser Val Trp Arg Tyr Asp Trp Val Thr Ser Tyr Lys Val Gln Phe  
 195 200 205  
 Ser Asn Asp Ser Arg Thr Trp Trp Gly Ser Arg Asn His Ser Ser Gly  
 210 215 220  
 Met Asp Ala Val Phe Pro Ala Asn Ser Asp Pro Glu Thr Pro Val Leu  
 225 230 235 240  
 Asn Leu Leu Pro Glu Pro Gln Val Ala Arg Phe Ile Arg Leu Leu Pro  
 245 250 255  
 Gln Thr Trp Leu Gln Gly Gly Ala Pro Cys Leu Arg Ala Glu Ile Leu  
 260 265 270  
 Ala Cys Pro Val Ser Asp Pro Asn Asp Leu Phe Leu Glu Ala Pro Ala  
 275 280 285  
 Ser Gly Ser Ser Asp Pro Leu Asp Phe Gln His His Asn Tyr Lys Ala  
 290 295 300  
 Met Arg Lys Leu Met Lys Gln Val Gln Glu Gln Cys Pro Asn Ile Thr  
 305 310 315 320  
 Arg Ile Tyr Ser Ile Gly Lys Ser Tyr Gln Gly Leu Lys Leu Tyr Val  
 325 330 335  
 Met Glu Met Ser Asp Lys Pro Gly Glu His Glu Leu Gly Glu Pro Glu  
 340 345 350  
 Val Arg Tyr Val Ala Gly Met His Gly Asn Glu Ala Leu Gly Arg Glu  
 355 360 365  
 Leu Leu Leu Leu Met Gln Phe Leu Cys His Glu Phe Leu Arg Gly  
 370 375 380  
 Asn Pro Arg Val Thr Arg Leu Leu Ser Glu Met Arg Ile His Leu Leu  
 385 390 395 400  
 Pro Ser Met Asn Pro Asp Gly Tyr Glu Ile Ala Tyr His Arg Gly Ser  
 405 410 415  
 Glu Leu Val Gly Trp Ala Glu Gly Arg Trp Asn Asn Gln Ser Ile Asp

420 425 430  
 Leu Asn His Asn Phe Ala Asp Leu Asn Thr Pro Leu Trp Glu Ala Gln  
 435 440 445  
 Asp Asp Gly Lys Val Pro His Ile Val Pro Asn His His Leu Pro Leu  
 450 455 460  
 Pro Thr Tyr Tyr Thr Leu Pro Asn Ala Thr Val Ala Pro Glu Thr Arg  
 465 470 475 480  
 Ala Val Ile Lys Trp Met Lys Arg Ile Pro Phe Val Leu Ser Ala Asn  
 485 490 495  
 Leu His Gly Gly Glu Leu Val Val Ser Tyr Pro Phe Asp Met Thr Arg  
 500 505 510  
 Thr Pro Trp Ala Ala Arg Glu Leu Thr Pro Thr Pro Asp Ala Val  
 515 520 525  
 Phe Arg Trp Leu Ser Thr Val Tyr Ala Gly Ser Asn Leu Ala Met Gln  
 530 535 540  
 Asp Thr Ser Arg Arg Pro Cys His Ser Gln Asp Phe Ser Val His Gly  
 545 550 555 560  
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 Glu Lys Arg Gln Gly Ala Lys Thr Val Phe Asn Lys Phe Ser Asn Met  
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 Asn Lys Trp Lys Lys Thr Glu Glu Thr Gln Glu Lys Arg Arg Ser Phe  
 85 90 95  
 Leu Gln Glu Phe Cys Lys Lys Tyr Gly Gly Val Ser His His Gln Ser  
 59/60

60/60



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(54) Title: **NOVEL COMPOUNDS**

(57) Abstract: Polypeptides and polynucleotides of the genes set forth in Table I and methods for producing such polypeptides by recombinant techniques are disclosed. Also disclosed are methods for utilizing polypeptides and polynucleotides of the genes set forth in Table I in diagnostic assays.

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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/09226

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) :C12N 15/12; C07K 1/00, 14/00

US CL :536/23.5, 530/350

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.5, 530/350

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN (Bioscience); East (all databases); sequence search, search terms: slit, leucine-rich repeat.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database GenEmbl, Accession Number AC009625, Whitehead Institute/MIT Center for Genome Research, Cambridge, MA, BIRREN et al. 26 August 1999.	1
A, P	Database Geneseq, Accession Number AAB07469, ZYMOGENETICS INC., A human leucine-rich repeat protein designated Zlrr3, WO200042184-A1, 20 JULY 2000, see sequence comparison, closest sequence homology.	1
A	WO 00/42184 A1 (ZYMOGENETICS INC.) 20 July 2000 (20-07-00), see entire document, especially SEQ ID NO:41.	1

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

"	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

16 NOVEMBER 2001

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US01/09226

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	NAKAYAMA et al. Identification of High-Molecular Weight Proteins with multiple EGF-like Motifs by Motif-Trap Screening. Genomics, 1998, Vol. 51, pp. 27-34.	1
A	BROSE et al. Slit Proteins Bind Robo Receptors and Have an Evolutionarily Conserved Role in Repulsive Axon Guidance. Cell. 19 March 1999, Vol. 96, pp. 795-806.	1

Form PCT/ISA/210 (continuation of second sheet) (July 1998)\*

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/09226

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2. ☒ Claims Nos.: 5-7  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:  
  
Claims 5-7 are not searchable because of improper claim dependencies.
  
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US01/09226

## BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

*This ISA found multiple inventions as follows:*

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group 1, claim 1, in part, drawn to the special technical feature of a polypeptide of SEQ ID NO:34.

Groups 2-33, claim 1, in part, drawn to the special technical feature of one of the 32 polypeptides of SEQ ID NOS: 35-66, respectively. If any of these groups are elected, Applicant must provide elected SEQ ID NO:.

Groups 34-66, claim(s) 2-4, in part, drawn to the special technical feature of one of the 33 polynucleotides of SEQ ID NOS: 1-33, respectively. If any of these groups are elected, Applicant must provide the elected SEQ ID NO:.

The species listed above do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons:

The nucleic acid molecules with the sequences set forth in SEQ ID NOS: 1-33 have different structural and functional features, therefore SEQ ID NO:1 will be searched. Applicants must pay appropriate fees for a search of each of the other SEQ ID NOS:.

The polypeptides comprising SEQ ID NOS: 34-66 have different structural and functional features, therefore SEQ ID NO:34 will be searched. Applicants must pay appropriate fees for a search of each of the other SEQ ID NOS:.

The inventions listed as Groups do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

There is no apparent shared common core structure and no apparent shared art recognized function. For example, the polypeptides and polynucleotides were isolated from different tissues, expressed in different tissues, and the polynucleotides encode polypeptides with varying function (various growth factors, matrix proteins, and proteases, for example).

Claims 5-7 are not searchable because of improper claim dependencies.

